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FUNCTIONS OF THE GALL-BLADDER

GALL-BLADDER function is a subject about which there has been a great deal of discussion and one that has been especially stimulated by many important discoveries in the United States.

The first of these was the duodenal tube, discovered by M. H. Gross and Max Einhorn independently in 1910, making it possible to obtain bile direct from the biliary tract. Next came Meltzer's announcement in a mere footnote to one of his articles that 33 per cent. magnesium sulphate, if applied directly to the sphincter of Oddi, might relax it and cause contraction of the gall-bladder. He based this assumption on the theory of contrary innervation which, he felt, should hold good in the gall-bladder as in any other viscus supplied with musculature and sphincter action and innervated by the vegetative nervous system. Lyon of Philadelphia at once applied this theory clinically by introducing 33 per cent. solution of magnesium sulphate through the duodenal tube and verified Meltzer's conception. Last, but not least, Graham, Cole, and Copher[21] published their epoch-making discovery of cholecystography in 1924.

It is surprising that, despite the many important facts pertaining to gall-bladder function brought out by these discoveries, there are still some who contend that the gall-bladder is a mere reservoir. Those who are of this opinion fall into three groups, the first basing their arguments upon the fact that the gall-

bladder is absent in certain animals like the horse, deer, rat, pocket gopher, dove, and peccary, and that it may be removed from the human with impunity and even with benefit in case of disease; the second group upon experimental data; and the third upon certain features of the anatomic structure of the gall-bladder, embryonically and in postfetal life.

As to the absence of the gall-bladder in certain animals, it is well known that in these animals the intrahepatic ductal system is much larger than in animals with a gall-bladder, and that the dilated ducts perform the functions of the absent gall-bladder. The removability of the gall-bladder from man with impunity does not disprove its function because, as Aschoff states so well, if removability of an organ were proof of want of function then one must assume that organs like the spleen, limbs, and teeth are functionless because the general well being of an individual deprived of them is unimpaired. The fact that certain organs in the body may be removed with impunity while others may not, would seem to justify a division of organs into two classes from the standpoint of function, namely, those that are *dispensable and those that are indispensable.*

Dispensable and Indispensable Organs.—The function of a dispensable organ after removal may be replaced by an accessory organ or by some compensatory mechanism in the body proper, or by artificial means. To give a few simple examples, if one kidney is removed the second kidney increases considerably in size and assumes its function. After splenectomy, the lymph-glands or the accessory spleens, or both, assume the spleen's function. Following cholecystectomy, as shown surgically by Judd in the Mayo Clinic and Schmieden in Germany, and experimentally in this country by Higgins, Bowman, Mann, Judd and Counsellor,[28] and by Rost[43] abroad, the common and small intrahepatic ducts dilate considerably in order to concentrate the bile and further its passage into the intestines, thus compensating for the absent gall-bladder. The rapid appropriation of the function of a removed organ may, at times, be detrimental to the individual. For instance, splenectomy as a remedy for some of the diseases affecting the hematopoietic system may be ineffectual

because either the existing accessory spleens or the lymph-glands continue the spleen's deleterious effect. This is true, also, after cholecystectomy if, as Schmieden has shown, the common duct dilates markedly after the removal of the gall-bladder and the sphincter of Oddi remains in a state of spasm, resulting in biliary colic of great severity. For this reason, Schmieden advises cutting the sphincter of Oddi at the time the gall-bladder is removed.

The classification of organs into *dispensable and indispensable* is clinically practical. The less dispensable an organ, the greater its reserve and so the liver, heart, kidneys, and lungs may be quite chronically diseased with but few subjective and objective symptoms. The finest functional tests often fail to reveal the true condition until, suddenly, the affected organ breaks down entirely.

This is not the case with a dispensable organ like the appendix, gall-bladder, or teeth which may be chronically diseased without giving rise to symptoms provided it has ceased to function. To illustrate, if the gall-bladder is entirely contracted and filled with stones, the common duct may dilate sufficiently to perform the function of the gall-bladder. On the other hand, if the diseased gall-bladder continues to function, it does so under protest and gives rise to symptoms out of proportion to the disease. The dispensable organs—more than the indispensable organs—may menace other organs of the body either by direct extension of the pathologic process to neighboring organ—or by harboring foci of infection which give rise to systemic disease. Hence, the diseased dispensable organ must be removed. From this, however, we do not wish the inference to be drawn that a dispensable organ like the gall-bladder should be removed if only suspected of being diseased, as happens so frequently. Mayo has shown that following a gastro-enterostomy on a stomach when there was no ulcer, the patient had more symptoms than before. This might be explained by the fact that when an operation is performed on a diseased stomach the accommodating power in the diseased organ proper or in those organs which possess accessory functions is well established and

continues after operation. If, on the other hand, the organ is not diseased at the time of operation and the symptoms that led to the operation did not lie in the organ proper, accommodation, being unnecessary, has never been present and the operation causes an injury. This is equally true of the gall-bladder. If removed in a chronically diseased state, the larger ducts have had time to accommodate themselves gradually and can continue their compensatory function to the advantage of the individual after the organ is removed. If a healthy gall-bladder is removed this accommodation—never having been established—is absent and new symptoms are superimposed upon those already existent.

Refutation of the arguments of the group of authors who rely upon experimental data for their assertion that the gall-bladder is functionless is difficult. And yet, it must be remembered, the average experiment is carried out under non-physiologic conditions and not all experimenters possess the necessary gifted technic or endurance for arriving at conclusive results. Those who, in the midst of their active clinical work, perform experiments under non-physiologic conditions and arrive at hasty conclusions add more to chaos than to order. This is true in almost every field of experiment, but conspicuously so within the last few years with regard to experimental work on the gall-bladder.

The functions of an organ, particularly the dispensable organ, are not alike in all animals and conclusions drawn from even the most exact experimental work on animals cannot be applied to the human. Experiments under such conditions are often misleading because a pathologic process is produced in which no accommodation is possible. This is not the case in human pathology, as a rule, except in extremely acute infectious diseases or disease due to acute poisoning or trauma. In human pathology the organ, by virtue of accommodation, assumes physiologic function as nearly as possible. Hence it may be stated that one of the important reasons why there is often a discrepancy between animal experimental results and clinical interpretation is that, in the former case, the experiment has caused pathologic

changes from which physiologic conclusions are drawn while the clinician actually deals with accommodated physiology.

The conclusions of those who have made experimentation their life work are naturally those to which we should attach greatest importance. Generally, their experiments are carried out under the most rigid conditions and the animal allowed to recover before further experiments are begun on the organ in question. In weighing experiments to prove or disprove gall-bladder function, we shall not present an account of the innumerable observations of a superficial character that have been made, but shall stress, instead, the results obtained by trained investigators and which would seem to be preponderantly in favor of gall-bladder function. It cannot be emphasized too strongly that when the results of experiments do not correspond with clinical observation, the clinician must give greater heed to clinical observation than to experiment. He must depend upon applied physiology which, although rather coarse, has proved sufficiently correct to be reliable.

Regarding the group who deny gall-bladder function on the basis of anatomic structure, among whom we find no less an authority than Carlson, it would seem that far from indicating a want of function the anatomic structure of the gall-bladder proves its very existence. To fortify this contention, let us briefly review the embryology and the most recent advances in our knowledge of the organ's anatomy.

EMBRYOLOGY

The gall-bladder, liver, and extrahepatic ducts originate in the endoderm. The gall-bladder itself is formed from a group of cells constituting the original cells of the liver, duodenum, and pancreas. The endodermal part of the liver, gall-bladder, and extrahepatic ducts projects like a diverticulum from the anterior wall of the foregut. This diverticulum, extending to the upper part of the mesoderm, is seen in the septum transversum, from the upper portion of which the diaphragm is formed and from the under portion the anterior mesentery. The hepatic cells originate from the hepatic diverticulum which re-

mains for the purpose of becoming hepatic ducts. The gall-bladder is a special subdivision of the original diverticulum while the ductus choledochus is an original part of the hepatic duct. The wall of the gall-bladder, consisting of connective tissue and smooth musculature, originates in the mesenchyme. The peritoneum and blood-vessels belonging to the gall-bladder form from the mesoderm. The nerve plexus originates from the ectoderm.

ANATOMY

Cystic Duct.—This duct is from 3 to 4 cm. long and enters the anterior wall of the gall-bladder. It has very scant musculature, but is rich in glands and elastic and nerve fibers. At its junction with the neck of the gall-bladder the mucous membrane is drawn into thick folds, first described by Heister and since known as valvuli Heisteri. These folds may, in certain instances, form such a narrowing between the cystic duct and the gall-bladder that, according to Schmieden, the passage of a thin probe meets with resistance. This is not without clinical significance for one may encounter hydrops of the gall-bladder as the result of the detention of a small mucus plug in this narrow passage, preventing the flow of bile into the gall-bladder. This condition was noted first by John Berg[4] of Sweden, who named it "mucostasis." According to Lutkens[33] the circular muscular fibers are increased where the cystic duct enters the gall-bladder and constitute a sphincter.

Common Duct.—The common duct starts at a point where both hepatic ducts unite and ends in the first portion of the duodenum at the papilla Vateri. One-third of the common duct lies above the duodenum and two-thirds behind it. Its length is from 9 to 10 cm., its breadth that of an ordinary lead pencil. In 90 per cent. of the cases the common duct passes through the head of the pancreas before it enters the duodenum. In such instances the slightest degree of swelling of the head of the pancreas compresses the common duct sufficiently to prevent the passage of bile into the duodenum and so gives rise to jaundice.

The lower part of the common duct has a scant supply of smooth musculature and is surrounded by pancreatic tissue. At

the point of the papilla Vateri where the common duct enters the duodenum, there are strong circular muscular fibers which were described by Oddi in 1887 as a sphincter and which have since been known as Oddi's sphincter. The existence of this sphincter has been verified by the careful anatomic studies of Hendrickson and Reach in this country.

According to Job[27] the musculature of the duodenal wall does not form a sphincter of the ducts, but the duct itself has an individual longitudinal and circular layer almost to the tip of the papilla. The common and individual muscular layers seem to mingle at various points.

Fig. 99. Fig. 100. Fig. 101.

Figs. 99–101.—Relationship of cystic and hepatic ducts.
Fig. 99.—Cystic duct parallel to hepatic duct.
Fig. 100.—Cystic duct parallel at acute angle to hepatic duct.
Fig. 101.—Cystic duct as spiral around hepatic duct. (After Kraus and Brugsch Spezielle Pathologie and Therapie by Kehr.)

The cystic duct normally runs parallel to the common duct (Fig. 99). At times the cystic duct forms an acute angle (Fig. 100) to the hepatic duct and occasionally forms a spiral around it (Fig. 101).

Gall-bladder.—The gall-bladder is a viscus consisting of mucosa, submucosa, and a muscular layer intertwined with a large number of elastic fibers, the greater part of which are covered by serosa.

William Boyd[7] found that rugæ or mucosal folds bind the polygonal spaces of the mucous membrane and give the interior a honeycombed appearance varying remarkably from distention to collapse. In certain parts it contains depressions known as

the Luschka ducts where, in case of gall-bladder infection, bacteria are harbored.

The fibromuscular structure consists of three layers: longitudinal, oblique, and circular. The development of the musculature is less in the fundus than in the neck. Both Boyden[8] and Lutkens found that there is much less musculature than elastic tissue. The subserous layer consists entirely of interlacing elastic tissue and fibrils. Boyden has shown that the connective-tissue layer under the serosa is nearly three times as thick as the submucosa, due, seemingly, to the richness of the elastic tissue in the coat. *The wall itself is rich in smooth musculature but poor in elastic fibers. This is important because if the exit of bile from the gall-bladder were not dependent upon the activity of the organ, but were, instead, a passive process, elastic fibers would predominate.*

Blood-supply.—The arterial supply of the gall-bladder comes from the cystic artery and from the arteries of that part of the liver to which the gall-bladder is attached. The blood is carried to the liver by the portal vein, thus explaining how bacteria can reach the portal vein and in case of severe infection of the gall-bladder give rise to septic thrombophlebitis of the portal vein. The branches of the portal vein are distributed like a network over the external surface of the gall-bladder. The lymph supply of the gall-bladder is of great practical importance. In the deep portions of the mucous membrane there is a fine network of small lymph follicles. In view of the fact that the muscles of the gall-bladder are rich in lymph follicles which connect directly with the liver cells, Graham, as well as Heyd, Killian, and McNeal, has concluded that in most cases of gall-bladder disease or infection there is a co-affection of the liver parenchyma.

Innervation.—The vagus and sympathicus constitute the main nerve supply of the gall-bladder and the ducts. Westphal demonstrated that the portal vein and hepatic artery are embedded in loose connective tissue derived from the celiac plexus and the fibers of the sympathetic nervous system. Small ganglionic nodes with groups of ganglionic cells are found in this reticulum as well as in the wall of the bile-ducts and in the

papilla Vateri. They seem analogous to the intramural nerve apparatus of the intestines and other viscera. These nerve filaments accompany the blood-vessels in the gall-bladder. In the connective-tissue bundles, the nerve endings form the basis of the blood-vessels, smooth musculature, and mucous membrane. The non-medullated Remak fibers are the main constituents of most of the nerve bundles. The weakly medullated fibers in the ligaments are derived from the spinal ganglion.

The arrangement of the nerve fibers in the wall of the gall-bladder and in the soft epithelial layer is considered by Aschoff as important as the intramural nerve fibers of the heart, stomach, intestines, and urinary bladder. According to Westphal,[52] there are intramural ganglion cells and nerve fibers in all biliary ducts which serve, to a certain degree, to regulate the motility and secretion of mucus in the gall-bladder and biliary duct.

FUNCTIONS

The **cystic duct,** by means of Heister's valves and the sphincter of Lutkens (loc. cit.) prevents the rapid passage of bile to and from the gall-bladder and serves to keep it there until it is needed in the process of digestion. Rous and McMaster[44] have pointed out that the mucous membrane of the cystic duct as well as of the other intrahepatic ducts can absorb fluids and lipoids almost as quickly as can the gall-bladder and that the dilution of bile is accomplished chiefly by the large hepatic ducts. The rich nerve supply of the cystic duct is very significant clinically and explains why even minor pathologic changes in this location may cause severe sensory disturbances. On the basis of animal experimentation, Menzer attributes little importance to the function of the valves of Heister, but it is quite likely that the anatomic structure of the cystic duct where the valves of Heister and the Lutkens sphincter are situated is different in the human than in the animal. Hence the discrepancy between experimental findings and observation, and an explanation of the want of stasis and stone in the gall-bladder of experimental animals.

The **common duct** is a passageway. Its main function rests in the sphincter of Oddi, as will be described later.

Mucous Membrane.—The filling of the gall-bladder occurs from the liver by way of the cystic duct. There is a constant dribbling of bile. A small part of the bile from the liver enters the intestines directly from the hepatic ducts, but the greater part, amounting usually from 1200 to 1500 c.c. in twenty-four hours, although, according to Brugsch, it may be more during the hot season, enters the gall-bladder. The question at once arises as to how the gall-bladder which normally holds 40 to 50 c.c. of bile can accommodate itself to so large a quantity of bile. In this respect absorption by the gall-bladder mucosa is of prime importance.

According to Boyd (loc. cit.) the most rapid absorption occurs in the partially collapsed gall-bladder. It is by virtue of absorption that the bile in the gall-bladder is concentrated 20 to 30 times more than liver bile, as was first shown by Hammersten, accounting for its dark color. Kalk[29] recently showed that at times the intrahepatic ducts and the liver may concentrate bile considerably. This has a practical value because dark bile is sometimes obtained from the intrahepatic ducts in the absence of the gall-bladder. Occasionally, the liver itself may concentrate the bile 20 to 30 times more than normal, but when it does the gall-bladder concentrates it 90 times.

After cholecystectomy the intrahepatic ducts (never the cystic duct) acquire this concentrative power. McClure[34] attributes the dark bile obtained from the intrahepatic ducts to a pigment in the bile that is insoluble in alcohol. He states that bile contains two kinds of pigment, one that is alcohol soluble and the other alcohol insoluble. If the former pigment predominates the bile is golden yellow; if the latter predominates it is dark. From McClure's work one may draw the clinical conclusion that the stronger the concentration of bile the more insoluble alcohol pigments it must contain. If the gall-bladder mucosa is diseased or if, after cholecystectomy, the concentrating function is taken up by the intrahepatic ducts or by the liver proper, dark bile may be obtained that is rich in alcohol insoluble pigments and, therefore, indistinguishable from gall-bladder bile.

The substances absorbed are water, bile pigments, lipoids

and, according to Rosenthal and Wislicki,[42] bile acids. Part of the lipoids are deposited in the gall-bladder in the form of cholesterol. According to William Boyd,[7] the normal gall-bladder contains 0.5 to 1.7 per cent. cholesterol. It is remarkable that even Virchow conceived the idea that the cells of the gall-bladder are concerned with the intermediary metabolism of fat. When there is a disturbance of fat metabolism, the gall-bladder mucosa is compelled to take up more fat than it can absorb. This excess fat is deposited on the wall of the gall-bladder in the form of cholesterol.

According to Aschoff the absorption of fat is an intravital process which occurs in the animal after milk is injected intravenously. Mentzer[39] studied the fat content of 633 gall-bladders; 46.4 per cent. showed an accumulation of lipoids in the gall-bladder wall. This explains how in the human the excessive intake of fat may cause a large deposit of cholesterol in the gall-bladder mucosa (an explanation of exogenous cholesterosis of the gall-bladder). Cholesterosis of the gall-bladder may also occur from an endogenous source in case of metabolic disturbance of fat absorption or when due to starvation as seen on the accompanying figure (Fig. 102).

A clinical diagnosis of cholesterosis, however, only because of the presence of a scant deposit of cholesterol is unjustifiable. Cholesterosis is present in almost all normal gall-bladders. It must be present to an excessive degree and be visible macroscopically before such a diagnosis is warranted for only when it exists abnormally does it interfere with the mucous membrane absorption of other substances and so lead to stagnation of bile and the formation not only of the solitary cholesterol stone but of mixed stones.

The proper absorption of pigment is exceedingly important clinically. McMaster[35] found that the bile of the liver of a mouse contains eight times as much pigment as that of a rat, which has no gall-bladder. Mann and Bollman[36] showed that when they ligated the common duct and left the gall-bladder intact, two or three days were required before jaundice developed. When the gall-bladder was removed, however, jaundice

occurred within several hours, showing that the bile pigment—the main constituent of jaundice—when it had no gall-bladder for its absorption, entered the blood and tissues and gave rise to jaundice much sooner than would otherwise have been the case. Clinically, this may explain the occasional formation of pigmented calculi in the intrabiliary and hepatic ducts after cholecystectomy. It also explains the well known clinical fact that when a patient suffers from a biliary attack due to stone in

Fig. 102.—Cholesterosis of mucous membrane of gall-bladder. (From Held-Gray, Die Krankheiten der Gallenblase; Ergebnisse der gesamten Medizin, x, Heft 1–2, 1927.)

the common duct or a supra-added inflammatory process with the gall-bladder present, jaundice does not develop usually before twenty-four to forty-eight hours. If biliary colic occurs after cholecystectomy due to common-duct obstruction, jaundice occurs almost instantly or within a few hours.

If bile that is richer in pigment than is normally the case reaches the gall-bladder, the unabsorbed pigment may be deposited in the gall-bladder mucosa and give rise to the formation of pigmented stones without any preceding infection or even

stagnation. This may occur in cases where there is marked hemolysis as, for instance, in hemolytic icterus or Addison-Biermer anemia or in chronic infections and other wasting diseases. In the presence of pigment deposits, absorption of cholesterol and perhaps salts may be secondarily disturbed, again leading to the formation of mixed stones without previous infection. Based on this, one may state that not only may the solitary cholesterol stone as pointed out by Aschoff be formed without previous gall-bladder infection, but mixed stones as well, as shown by Rovsing.

According to Rous and McMaster[44] inorganic substances and water are absorbed partly by the lymphatics, but chiefly through the blood. In order that they may be absorbed the concentration power of the gall-bladder must be such as to reduce the bile to 20 per cent. dry substance. If the concentration is greater than 20 per cent., solid particles are deposited in the gall-bladder thus explaining why the mucosa may not be even microscopically diseased and yet, in the presence of strong concentrating power, fail to cast a shadow. That the concentrating power of the mucosa must be intact to cast a shadow with the dye has been demonstrated experimentally by St. Kartal.[30] When the bile in the condom was diluted to 0.16, 0.18, or 0.22, no shadow was obtained. When it was concentrated from 2 to 6 per cent. a shadow was distinctly visible.

Some authors, notably Sweet, Halpert, and Blond, are of the opinion that absorption is the gall-bladder's only function. That is to say, bile enters the gall-bladder and some of its absorptive substances are taken up by the polygonal cells, others are reabsorbed by the liver, but none ever leaves the gall-bladder. According to these authors, the bile that enters the intestines does so directly from the liver through the hepatic duct. Their work is unusually interesting and deserves careful study because each has contributed a great deal to our knowledge of the pathology of the gall-bladder. Sweet's[50] contributions regarding stone formation are most valuable.

Halpert[23] points out rightfully that a disturbance of absorption may result either from pathologic bile excreted by a dis-

eased liver or from disease of the mucous membrane of the gall-bladder. In either case, stasis of bile in the gall-bladder results, leading to stone formation. If the absorptive function is disturbed because diseased liver bile reaches the gall-bladder, Halpert terms the condition "hepatogenous"; if the disturbance is due to a disease of the mucosa itself he terms it "cystogenous." The muscular layer, according to Halpert, serves only to draw the mucous membrane into folds. He regards the sinuses, described by Rokitansky and Aschoff and considered by them to be present in the normal human gall-bladder, as outcroppings of the mucosa into defects of the muscularis. The most favored sites of such sinuses are where the vessels penetrate the muscularis in order to reach or leave the mucosa. Halpert looks upon these sinuses as indications of disease.

Blond[6] bases his opinion that part of the gall-bladder bile is reabsorbed into the liver and that none of it enters the intestines from the gall-bladder on the fact that the cystic vein empties into the portal vein so that the blood of the gall-bladder has to pass through the liver on its way to the heart.

There is no doubt that some of the pigments as well as some of the salts are reabsorbed by the liver. It is certain that some of the bile regurgitates into the liver through the cystic duct, for cholecystography has demonstrated beyond doubt that part of the dye is reabsorbed by the liver. Areas of dye in the liver are often seen twenty-four hours after the administration of the dye and long after the gall-bladder has emptied itself. It is well known that four to six or even eight hours after the oral administration of the dye the liver may show a considerable quantity of the dye. Stewart utilizes this phenomenon to demonstrate liver metastasis. He states that dye seen four to eight hours in the liver before it enters the gall-bladder may be of sufficient density to make possible the differentiation of individual nodules characteristic of tumors. It is our opinion that the cancer cells eliminate the dye much more slowly than does the normal liver. Hence the greater density of shadows over the areas where the tumor masses are present. Such a density may persist far beyond the normal time.

Except Sweet, Halpert, and Blond, all who have worked in this field agree that the gall-bladder periodically empties a good part of its contents in concentrated form through the cystic duct and the sphincter of Oddi into the intestines, and that this periodic emptying depends upon a great many factors among which may be mentioned the intake of food, particularly the kind of food, fat having the greatest influence upon gall-bladder emptying, proteins next, and carbohydrates least.

Clinical proof that a good part of the bile periodically passes into the intestines from the gall-bladder has been made possible by the Lyon method of biliary drainage and the epoch-making discovery of cholecystography by Graham, Cole, and Copher. Lyon was the first in this country to show that one can differentiate, by biliary drainage, between the so-called "B-bile" coming from the gall-bladder and that coming from the liver and ducts. The gall-bladder bile is much more concentrated, is richer in pigments, has a higher specific gravity, and a lower specific density, and frequently contains cholesterol crystals. The findings of Lyon, however, have not gone without contradiction. Bassler, Luckett, and Lutz[3] deny that it is possible to prove the vermicular action of the gall-bladder or that contractions take place, or that the characteristic dark-colored bile is obtained from the gall-bladder. They came to this conclusion after examining four operative cases with the duodenal tube *in situ*. When the patients were under anesthesia and with the duodenal tube *in situ* into which an installation of magnesium sulphate was made during the operation they were able to obtain dark bile which was not proved to be that from the gall-bladder. Cholecystectomized individuals show the characteristic B-bile shortly after operation before the ducts have a chance to dilate. This occurs so commonly, according to these authors, that B-bile cannot always be from the gall-bladder.

Matsuo,[37] who carried out similar experiments under anesthesia, could not obtain dark bile after cholecystectomy which, according to him, proves that without the gall-bladder no dark bile can be obtained. The difference in the results obtained by Bassler, Luckett, and Lutz tends to prove the degree of caution

we must exercise in examining and accepting the results obtained from experiments carried out under anesthesia.

Some argue that the dark bile is not gall-bladder bile because, months after cholecystectomy, on some patients, dark bile like that coming from the gall-bladder can be obtained. However, it is well known, as already stated, that very often after cholecystectomy the common duct as well as the hepatic ducts dilate sufficiently to take over the concentrating function of the gall-bladder to a certain degree. This would explain, too, how dark bile can be obtained in those very rare cases where the gall-bladder is congenitally absent.

M. H. Gross in the year he invented the tube had occasion to study a patient with hydrops of the gall-bladder. The gall-bladder emptied its contents while he had the duodenal tube *in situ*. When examining a patient with hydrops of the gall-bladder with symptoms of a nature to indicate operative intervention, the gall-bladder may be palpated while the patient is under anesthesia. Yet, when the abdomen is opened the gall-bladder may be entirely collapsed. This can only be explained by the fact that either during anesthesia the sphincter relaxed or a stone in the cystic duct suddenly dislodged itself so that the gall-bladder emptied. That the absorption of bile in the gall-bladder alone could cause the gall-bladder to collapse between anesthesia and the opening of the abdomen can hardly be conceived.

Another very important proof of gall-bladder emptying has been furnished by Kalk (loc. cit.). With the duodenal tube *in situ* shortly before operation he obtained bile and determined its color and concentration. When the patient was under anesthesia he punctured the gall-bladder with a thin needle and obtained bile which proved to be identical in color and concentration to that which he had obtained before operation through the duodenal tube.

Matsuo, Todo, and Nakashina injected azorubin and then magnesium sulphate through the duodenal tube and obtained red bile. As the bile from the cystic duct was white, the red bile could not have come from there.

Kawashina[31] injected indigo carmin into the gall-bladder and common duct. He also injected acetylcholin. He noticed first a yellowish blue bile. Finally, there was a cessation of the bile flow. After two and a half hours he opened the ductus choledochus and found yellowish-blue bile. He reinjected acetylcholin and there was an increase of yellowish-blue bile. Autopsy revealed blue discoloration of the gall-bladder, a weakly blue cystic duct, and slightly blue choledochus. The ductus hepaticus was blue only in the part close to the cystic duct.

Ellinger introduced a cannula into the common duct of dogs under novocain and ether narcosis and injected peptone. There was an increased flow of dark bile. This work laid the foundation for the studies of Stepp.

Our own studies have convinced us that the Lyon method of biliary drainage makes it possible to obtain bile directly from the gall-bladder using magnesium sulphate, Stepp's 5 to 10 per cent. peptone, Trummer's 10 to 20 per cent. glucose solution, the injection of olive oil, or at times, by the subcutaneous injections of pituitrin.

Further evidence of the fact that gall-bladder bile can be obtained by biliary drainage lies in the fact that typhoid bacilli may be cultured in the bile of individuals whose gall-bladders contain such organisms either because they are typhoid carriers or suffer from cholecystitis due to typhoid bacillus infection.

Cholecystographic Proof of Emptying.—Boyden injected lipiodol and iodopin into the gall-bladders of animals and then closed the abdomen. When the animals recovered he fed them yolk of egg or injected cholin or pituitrin and made radiographic studies. He found that three minutes after egg yolk, iodopin appeared in the cystic duct, five minutes later in the choledochus, and seven minutes after that in the small intestines, indicating that the gall-bladder empties itself. He also showed that a fat meal in man brings about a considerable reduction of the gall-bladder shadow, proving conclusively that the gall-bladder empties.

Whitaker and Maddock[54] ligated the common duct of an animal and injected phenoliodotetraphthalein. They radio-

graphed the animal repeatedly during twenty-four hours and the gall-bladder was persistently filled. After removing the ligature, they again radiographed the animal and found that the gall-bladder had emptied itself, showing that emptying must take place through the common duct.

Copher likewise demonstrated that the gall-bladder empties through the common duct when he ligated the cystic duct after the gall-bladder was filled with dye. The gall-bladder contained the dye for a full week, the period of time the duct was ligated. When he ligated both the cystic and common ducts the gall-bladder contained the dye three weeks after the animal was killed.

Menees and Robinson[38] as well as Whitaker have furnished clinical proof that the gall-bladder does not empty its contents in case of common duct obstruction. They had occasion to observe a patient with gall-stones after the cholecystographic shadow was obtained. The shadow persisted twenty-one hours and proved to be due to obstruction of the common duct by stone, thus preventing the emptying of the gall-bladder.

Sosman, Whitaker, and Edson[48] experimented on medical students in Harvard University and found that the gall-bladder empties its contents into the duodenum in response to certain foods. Fat almost completely emptied it, peptone and lean meat emptied it slowly, but the white of egg caused no emptying. Pure olive oil reduced the size of the gall-bladder in dogs but not in man. Bicarbonate of soda increased the density of the gall-bladder shadow. Physostigmin, pilocarpin, pituitrin, and adrenalin caused it to empty; diluted hydrochloric acid given by mouth or through the duodenal tube, nitroglycerin, meat extract, also given by mouth or tube, cinnamon, starch foods, and sugar had a variable influence.

Silverman and Manville[47] were able to show cholecystographically that by means of magnesium sulphate the gall-bladder can empty itself. Bernstein and Held[5] also showed that magnesium sulphate or peptone administered through the duodenal tube causes considerable reduction in the size of the gall-bladder (Figs. 103–106).

Fig. 103.

Fig. 104.

Figs. 103, 104.—Effect of magnesium sulphate upon the emptying of the gall-bladder.

Fig. 103.—Before drainage.

Fig. 104.—After drainage.

Fig. 105.

Fig. 106.

Figs. 105, 106.—Effect of peptone upon reduction of the size of the gall-bladder.

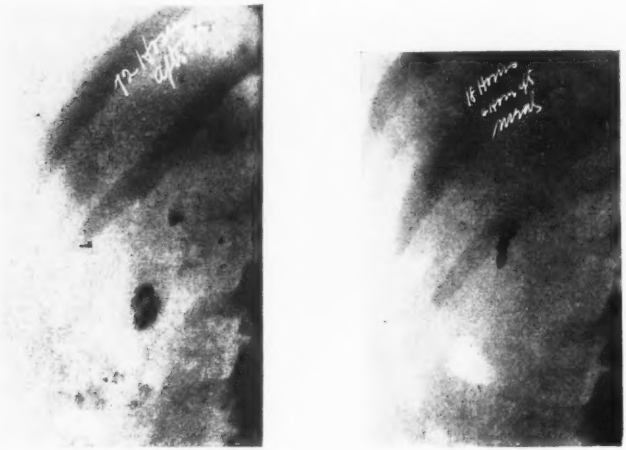
Fig. 105.—Before the injection of peptone.

Fig. 106.—After the injection of peptone.

Dark bile was obtained through the tube. These facts can be explained only on the ground that the gall-bladder empties itself.

It can be demonstrated cholecystographically that in many cases the ordinary buttermilk-barium meal causes considerable emptying of the gall-bladder.

H. Brunner[13] contributed further cholecystographic proof of the emptying function of the gall-bladder when he showed recently that stones in the gall-bladder assume a different position after the gall-bladder is reduced in size by means of a fat meal. We have made similar observations (Fig. 107).



A B

Fig. 107.—Different positions of gall-stones after emptying of gall-bladder by fat meal. A, Twelve hours after the dye. B, Eighteen hours after the dye and four hours after the administration of a fatty meal.

If absorption alone were the cause of gall-bladder emptying, the size of the gall-bladder would be reduced soon after the entrance of the bile because absorption is a spontaneous process. Or, in view of the fact that there is a continuous dribbling of bile into the gall-bladder, the size would be uniform just as the water in a well, filled by a stream, remains at a given level as long as the stream continues to flow. Cholecystographic studies, however, have taught us that this is not the case. The reduction in the size of the gall-bladder after the intake of a

meal is not alike in all individuals, requiring usually half to one hour, and may vary even in the same individual.

Clinical proof that the gall-bladder contents pass through the common and cystic ducts upon leaving the gall-bladder is shown by the fact that the surgeon often encounters a stone caught in the common duct at its exit into the duodenum or in the cystic duct. Furthermore, stones of considerable size (large enough to cause intestinal obstruction) are encountered frequently in duodenal contents and recovered from the stool. They could be there only if the gall-bladder empties itself into the small intestines. The surgeon in testing the passageway of the bile from the gall-bladder can often squeeze bile from the cystic and common ducts into the intestines.

How Does the Gall-bladder Empty?—Granting that the gall-bladder does empty, the question at once arises as to whether the process is passive or whether it is governed, as Meltzer expresses it, by the law of contrary innervation, that is to say, by contraction of the gall-bladder and relaxation of the sphincter of Oddi.

There are some who believe that the process is passive. No less an authority than the great physiologist, Carlson, found that even during a state of hunger bile seemed to pass into the intestines, depending upon the muscular tone and the periodic contractions of the duodenum, and that neither the gall-bladder nor the sphincter of Oddi plays an important rôle.

Haberland[22] believes that emptying is largely a passive process due to pressure of surrounding organs. He bases this conclusion upon the fact that while operating on patients under anesthesia he has never succeeded by any known methods such as electric stimulation or pinching the organ, in noting any contraction or diminution of the size of the gall-bladder to indicate that bile had left it.

This argument can be contradicted. It is well known, as pointed out above, that during anesthesia many functions in the body are disturbed. Knee and pupillary reflexes are lost, not due to spinal disease. Even large organs like the stomach when operated upon with the patient fully anesthetized are

seldom seen to relax and do not respond with contractions to electric or other stimuli. Moser[40] observed a case operated on under spinal anesthesia. After the bile was aspirated from the gall-bladder, active contractions of the gall-bladder took place.

Copher, Kodoma, and Graham[17] state that the gall-bladder empties by means of the elastic recoil of the distended viscus which relaxes the common-duct sphincter, and contend that the entrance of bile into the duodenum is due to increased tone in the duodenum proper. In other words muscular contraction of the duodenum causes the gall-bladder to empty. They fortified their conclusion experimentally by replacing the gall-bladder of a dog with a thin rubber bag attached to the cystic duct. Using a short glass cannula, they administered the dye and obtained a cycle of shadows by the artificial gall-bladder almost like those of the normal human gall-bladder. Because such interchange (a considerable factor in emptying) is associated with the gall-bladder's ability to distend and recoil and with the periodic action of the sphincter and common duct, they are convinced that it is the elastic and not the contractile power of the wall that aids in the release and contraction of the coil. They attribute importance to the muscular contraction of the duodenum and some importance to the cystic and common ducts. Burget,[14] as a result of his experimental work, has arrived at similar conclusions.

Sufficient evidence to contradict the assumption of these authors has been furnished by the excellent experiments of Whitaker, who demonstrated that the suction process and contraction of the duodenum do not, alone, play an important rôle in emptying the gall-bladder. Boyden (loc. cit.) severed the duodenum from the gall-bladder and demonstrated that the emptying of the gall-bladder in response to food was exactly as before the duodenum was severed. The small rôle played by the contraction of the first portion of the duodenum is due most likely to a hormone described by Ivy and Oldberg.[26] This hormone, which Ivy and Oldberg call cholecystokinin, is a chemical substance that differs from pancreatic secretin and yet, like it, is generated in connection with the upper intestinal

mucosa. When acid is injected into the duodenum, some substance enters the blood and causes the gall-bladder to contract. Ivy and Oldberg supplemented these observations by cross circulation experiments where the introduction of fat into the duodenum of one animal caused a substance to enter the blood which passed, by means of the cross circulation cannula, into the second animal and caused its gall-bladder to contract. They found that the process of evacuation is successful if the resistance of the sphincter is overcome by the contraction of the gall-bladder. If the duodenum were spastic, it is quite likely that the gall-bladder would not evacuate, although caused to contract by cholecystokinin. This may explain some of the reports of negative results observed after the introduction of acid into the duodenum of man. Ischiama also found a hormone of a cholin nature in the gall-bladder altering the effect of adrenalin and stimulating the activity of the ganglion cells in the gall-bladder wall.

Clinically, it is inconceivable that contraction of the duodenum could be the main factor in emptying the gall-bladder. It is known that the rapidity with which the gall-bladder empties depends a great deal upon the kind of food ingested. Furthermore, it has been shown by Carlson that there are hunger contractions in the stomach and duodenum. If contraction of the duodenum, therefore, were the sole causative factor in gall-bladder emptying, the outflow of bile into the small intestines would be as great after the intake of carbohydrates as after fat. Also, during a state of hunger the gall-bladder would be empty. In reality, the reverse is true. After carbohydrates there is very little emptying of the gall-bladder and in a state of hunger it is full. Whereas we must accept the fact that the elastic fibers of the gall-bladder do cause it to distend in order that it may accommodate itself to its contents, nevertheless its emptying must depend to a large degree upon musculature contraction.

Some authors, basing their conclusions upon animal experimentation, attribute important function to the sphincter of Oddi, but deny any importance to contractility of the gall-bladder. The act of respiration, particularly the activity of

the diaphragm, has been rightfully considered an important influence upon the activity of all abdominal viscera. Hofbauer has assumed that the activity of the diaphragm is one of the main factors in influencing emptying of the gall-bladder. Winkelstein and Aschner,[55] experimenting extensively, have arrived at the conclusion that increased gall-bladder pressure to overcome that of the sphincter of Oddi in the course of the expulsion of its contents into the duodenum, is not brought about by contractility but by the act of respiration, especially the action of the diaphragm. They attribute important function to the sphincter of Oddi.

From a clinical standpoint, Winkelstein and Aschner's contribution is essential because we know that in prophylaxis and treatment of gall-bladder disease anything, such as tight corseting, that interferes with the act of respiration is liable to lead to stagnation of bile, infection, and even stone formation. It is impossible to concede, however, that the emptying of an organ—especially the gall-bladder, two thirds of which is embedded in the liver—depends exclusively upon respiration and the action of the diaphragm.

In fact, Higgins and Mann[25] have proved conclusively that the action of the diaphragm cannot play a sole rôle in the emptying of the gall-bladder. They showed that in the gar pike, where respiration is by gills without a diaphragm, the gall-bladder empties ingested fat as in other mammals. In addition to experimental evidence, there is sufficient clinical proof that emptying of the gall-bladder is often independent of the action of the diaphragm. In cases where the mobility of the entire right side of the diaphragm is interfered with on account of pleurodiaphragmatic adhesions, acute infection of the right pleura and lower lung, traumatic paralysis of the diaphragm due to injury of the vagus, diaphragmatic hernia or a subdiaphragmatic abscess, emptying of the gall-bladder is not hindered.

Proof that active contraction of the gall-bladder is of vital importance in the act of expelling the bile is furnished in the following ways:

(*a*) Anatomic structure.

(*b*) Experimental data.
(*c*) Biliary drainage.
(*d*) Cholecystography.
(*e*) Clinical evidence.
(*f*) Pathology.

Anatomic Structure.—As a description of the anatomy of the gall-bladder, lymphatics, and nerve supply, was given above, it will not be repeated here. Like all other viscera the gall-bladder has an important nerve supply from the vegetative system sufficient to influence motility and secretion, and the sphincter has an ample supply to cause its contraction and relaxation. There is an intramural nerve supply following the smallest vessels as in the case of all viscera to insure the autonomy of the organ. Even without direct experimental proof, it would be most unreasonable to assume that an organ so richly endowed with elastic fibers, musculature, glands, nerves, blood-vessels, and lymphatics should be functionless. Experimental proof of its function, however, is abundant, filling volumes. Only the most important experiments are presented.

Experimental Data.—Eiger demonstrated experimentally that the vagus is the secretory nerve of the gall-bladder and that its motor fibers supply the bile-ducts. By stimulating the vagus fibers he succeeded in bringing about an increase in the flow of bile and the closure of the sphincter of Oddi. He also showed that morphin and nicotin increase the tone of the sphincter of Oddi.

Reach[41] experimented with guinea-pigs and demonstrated that papaverin causes dilatation of the sphincter, but pantopon, adrenalin, and morphin cause contraction. The observation that morphin causes a spasm of the sphincter has an important clinical bearing, explaining why in certain cases of biliary colic, morphin increases the pain. It is worth remembering that in such cases scopolamin and papaverin are far more useful. The experiments of Eiger and Reach regarding the effectiveness of various drugs in causing relaxation and contraction of the sphincter have been confirmed by Winkelstein and Aschner. Lieb and McWorter obtained isolated gall-bladder contractions

when they applied pilocarpin, physostigmin, and barium chlorid, and relaxation upon the application of atropin, nitrites, bile salts, and pituitrin.

Bainbridge and Dale[2] introduced a rubber ball into the gall-bladder and by stimulating the splanchnic nerve produced an inhibitory effect upon it. When the splanchnic nerve was cut rhythmic contractions resulted. When the peripheral end of the vagus was stimulated the gall-bladder contracted, thus demonstrating that the vagus is also the motor nerve of the gall-bladder.

Westphal[52] has shown that the muscular apparatus and innervation of the sphincter of Oddi are analogous to the pyloric part of the stomach. He likens the duodenal portion of the sphincter to the pyloric part of the antrum, and the sphincter ring on the papilla Vateri to the pyloric ring. The duodenal portion receives fibers from the vagus nerve, the influence of which is stimulating, and from the sympathicus, which is inhibitory. The ring portion is stimulated by the sympathicus and inhibited by the vagus. The upper duodenal portion is mostly open and filled with bile. When gall-bladder contraction takes place this part dilates, whereas the lowest portion of the sphincter contracts and spurts bile periodically through the open sphincter into the duodenum. During this process Westphal observed definite peristaltic activity in that part of the musculature of Oddi which he compares to the antrum of the stomach.

Westphal has also demonstrated experimentally that the emptying of the gall-bladder depends upon the proper relation of the tone of the gall-bladder to that of the sphincter. If he stimulated the vagus of the gall-bladder, bringing about a hypertonus of the organ, and simultaneously stimulated the sympathicus of the sphincter so that the sphincter remained in a state of spasm, no bile was seen to leave the gall-bladder. If he stimulated the sympathicus so that the gall-bladder was in a state of atony with the sphincter of Oddi under the influence of the sympathicus and therefore in a state of spasm, no bile could leave the gall-bladder.

He deduced from this important experiment that if there is

innervation-disturbance in the gall-bladder of the human so that the sphincter of Oddi does not relax when the gall-bladder contracts, stagnation of bile results. He termed this, in the human, *dyskinetic dysfunction of the gall-bladder*. If the gall-bladder is in a state of hypertonus and the sphincter of Oddi is likewise spastic, he terms the condition *cholecystophatica hypertonica*. On the other hand, if the gall-bladder is atonic and the sphincter is spastic, he applies the term *cholecystophatica hypotonica*. Either condition may be of a purely functional neuropathic nature of constitutional or acquired origin and may give rise to symptoms simulating organic disease, leading to surgical intervention with the surgeon encountering perfectly normal conditions when the patient is under anesthesia.

Giordano and Mann[20] examined several specimens at necropsy and found that the sphincter mechanism can be thrown into spasm by pathologic conditions in the gastro-intestinal tract and adjacent organs.

The spasm of the sphincter of Oddi may be so marked and the passage of bile into the small intestines so hindered that jaundice of considerable degree and an elevation of temperature may result. If this condition persists stagnation of bile in the gall-bladder with infection and possible stone formation may take place. This neurogenic functional condition, according to Westphal, may give rise to organic disease. The neurogenic theory of biliary colic, gall-bladder stasis, and even stone formation is here furnished.

Direct Visualization of Gall-bladder Contraction.—Chandler and Nevell[16] have demonstrated that the contents of normal gall-bladders are expelled by active muscular contractions.

Boyden ligated the choledochus between the exit of the cystic duct and the entrance of the hepatic duct and injected barium cholin into the gall-bladder. He noticed that the contrast substance in the liver could take place only under active gall-bladder contraction.

Chiray and Pavel[15] placed a gall-bladder in Ringer's solution to which one-third defibrinated blood had been added and registered its movements kimographically. Two kinds of con-

traction were noted: a prolonged slow contraction that was tonic and a rapid one, more difficult to bring about. Pilocarpin and eserin increased and prolonged the first kind. Pilocarpin alone produced rapid contraction. These authors have called attention to the fact that indigo-carmin and methylene-blue, to a lesser degree, take hours to defundate through the entire bile. This explains how the dye may remain for days in the fundus despite gall-bladder contraction.

Brugsch and Horsters,[12] working with methyl cholin, histamin, and ergotamin on the isolated gall-bladders of guinea-pigs, noticed that the longitudinal contractions were more outspoken than the circular.

Taylor and Wilson[51] demonstrated that the gall-bladder contracts when they opened the abdomen of a dog under anesthesia and introduced a balloon into the gall-bladder. When the animal recovered they were able to observe that under pressure of 5 to 15 c.c. of water in 60 per cent. of cases, rhythmic contractions of the gall-bladder were registered after one hour. To be sure that the increased pressure was not occasioned by the surrounding organs, they separated the gall-bladder from the liver and placed it in a glass tube. From six to twelve contractions were noted. The contractions were increased by adrenalin and stopped by morphin and apomorphin. They were also increased by 10 c.c. of one-tenth normal hydrochloric acid. The introduction of 40 c.c. of 33 per cent. magnesium sulphate or $\frac{1}{2}$ c.c. pilocarpin intraduodenally increased the tonus of the gall-bladder and relaxed the sphincter considerably.

Doyon found that the pressure in the common duct under which bile is expelled is 60 to 80 mm. water and 120 to 130 mm. water in the sphincter. Elman and McMaster[18] found that the resistance to the flow of bile in the sphincter region during a state of hunger is as high as 300 mm. water, but a few minutes after the administration of food falls to 100 or 120 in the sphincter. These authors, as well as Taylor and Wilson, measured the pressure in the gall-bladder after a meal and found an increase of 100 to 200 mm. accompanied by rhythmic contraction waves.

Westphal and Schoendube[53] ligated the hepatic duct of the gall-bladder of an animal when it was at a standstill. They clamped the cysticus and injected bilirubin and noticed increased pressure in the gall-bladder, attributable only to contractions of that organ. They also noted contractions of the gall-bladder on the application of barium chlorid.

The most conclusive experimental proof of the contractile activity of the gall-bladder as a means of emptying the organ, has been furnished by Higgins and Mann (loc. cit.). They ligated the hepatic ducts of dogs near the junction of the common duct and sutured a rubber catheter into the common duct about 2 cm. from the ampulla. A small rubber T-tube was then sutured into the duodenum near the ampulla to provide a means of feeding. The rubber catheter, previously filled with water, was connected with a pressure manometer and for one hour no bile appeared in the manometer or catheter despite the fact that sphincter control had been removed. After the gradual administration of 260 c.c. of test food, the water in the manometer rose for thirty minutes, followed by dark-brown bile unquestionably of the gall-bladder type. The pressure was gradually increased proving that the gall-bladder was emptying by a series of contractions.

The exit of bile from the gall-bladder was entirely independent of respiratory fluctuations. Coincident with the small fluctuations, yet entirely independent, was a large more retarded one, induced by the contractility of the vesicle itself.

Three hours after the injection of the first food into the duodenum, the gall-bladder gained its maximum pressure, 200 to 225 mm. of bile. As the bile was withdrawn the pressure rose to 50 mm. of bile. When this was withdrawn, there was no further evidence of bile in the catheter, indicating that the gall-bladder had ceased its emptying process. This cessation occurred four to four and a half hours after the first feeding.

The animals were killed and the gall-bladders were found partially filled. The actual quantity of bile expelled from the vesicle was 60 per cent. of its contents. Higgins and Mann's comparison of the total capacity of the gall-bladder with the

amount of bile removed do not offer much in support of the absorption hypothesis. During four and one half hours' active digestive procedure, one would expect a considerable quantity of bile to be absorbed by the walls of the vesicle. This, however, did not occur. These authors attribute more importance to the contractile power of the gall-bladder than to the resistance and relaxation of the sphincter of Oddi.

Higgins and Mann's experiment is of vital clinical import, explaining, why after cholecystectomy even though the sphincter of Oddi is functionless, the flow of bile into the intestines from the common duct may be impeded, so leading to dilatation of the common and even of the smaller intrahepatic ducts. Although the resistance of the sphincter of Oddi is removed the bile still needs a certain amount of pressure in order to flow out. This pressure can be exerted only by gall-bladder contractions.

Biliary Drainage.—The work of Stepp,[49] who showed that 5 to 10 per cent. peptone injected intraduodenally causes the bile to empty, and the work of Schoendube and Kalk[45] concerning the influence of 1 c.c. pituitrin intramuscularly is further proof of gall-bladder contractions.

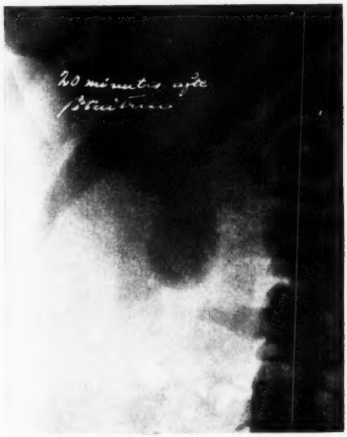
Our experience with peptone has been such that, like Stepp and others, we have found that the gall-bladder empties in the majority of cases as shown in Figs. 105, 106.

Our experience with pituitrin has not been so uniform. In reality, in most cases it has been a disappointment (Fig. 108, A, B, C).

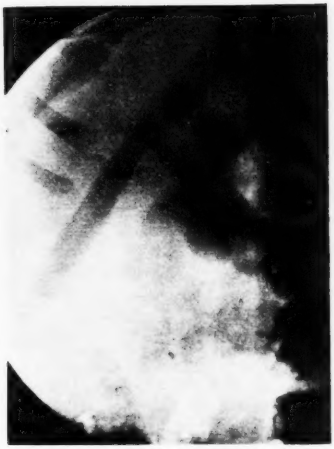
Kalk,[29] who is so enthusiastic regarding the effectiveness of pituitrin on the emptying of the gall-bladder, advocates its employment in biliary stasis and stagnation of bile in the gall-bladder, particularly of the atonic type. He states that the failure of Bernstein and Held to get any response from pituitrin must have been due to the fact that the duodenal tube was not *in situ*. Figure 109, A, B is only one of many of its kind showing that the duodenal tube *was in situ*. Although Bernstein and Held used pituitrin according to the directions given by Kalk and Schoendube they did not succeed in causing the gall-bladder to empty as often as did Kalk. We do not, however, deny the

fact that pituitrin causes the gall-bladder to contract and so aids it to empty its contents, and we believe that in biliary stasis due to an atonic condition of the gall-bladder the use of pituitrin is indicated.

A



B

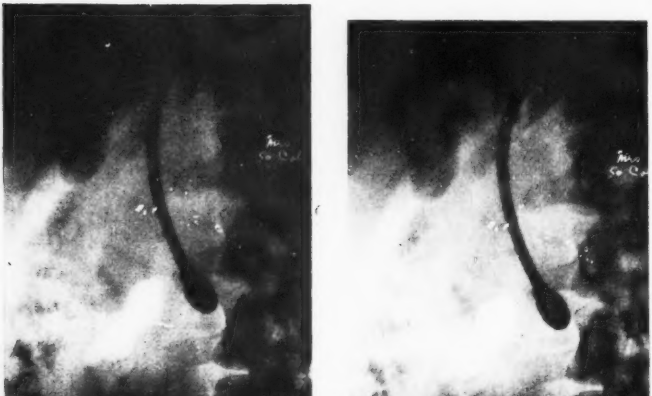


C

Fig. 108.—The effect of pituitrin on the gall-bladder. A, Before the injection of the drug. B, Twenty minutes after injection. C, One hour after injection.

Regarding the effect of pituitrin on the gall-bladder the

experimental work of Adlersberg is unusually interesting. He showed in animals that if chlorotone were administered before pituitrin in order to paralyze the base of the brain pituitrin failed to empty the gall-bladder. Other narcotics, such as paraldehyd, which affects the cortex of the brain, had hardly any influence. Luminol had a slight influence. Adlersberg found in man that if chlorotone is administered one-half hour before the injection of pituitrin no bile can be obtained from the gall-bladder by biliary drainage.



A B

Fig. 109.—Showing the duodenal tube *in situ*. A, Before injection of pituitrin. B, One hour after injection, showing little effect and slight contractions.

This experiment tends to show that pituitrin exercises its influence upon the expulsion of bile from the gall-bladder through the central nervous system, particularly through the base of the brain. In other words, it is a drug that causes kinetic action of the gall-bladder and is, therefore, a choleretic, in contradistinction to bile acids which cause choleresis, or the direct flow of bile from the liver into the gall-bladder. The influence of pituitrin on the gall-bladder in this respect is analogous to the find-

ings of Hoff and Werner regarding its influence on diuresis. In case of brain tumor or postencephalitic brain lesion, pituitrin loses its effect on diuresis. The conclusion may be drawn that in those cases where pituitrin does not bring about a gall-bladder reflex, this failure may be due to temporary functional disturbance in the central nervous system.

Another important clinical deduction to be derived from Adiersberg's work is that when pituitrin and bile acids are employed in the treatment of gall-bladder disease they must not be administered simultaneously. The choleresis producing bile acids should be administered at least half an hour to one hour prior to the choleretic pituitrin.

Schoendube and Lurmann[46] found that morphin likewise interfered with the reflex action of pituitrin. But this is not by way of the nervous system, but is the result of the spasm of the sphincter of Oddi produced by morphin, thereby interfering with the expulsion of bile by the gall-bladder.

Cholecystographic Proof of Gall-bladder Contraction.—Cholecystography has aided a great deal in establishing from both experimental and clinical standpoints that contraction of the gall-bladder is very important in the process of emptying. It is true that fluoroscopically contractions are rarely seen. There are, however, two reasons for this: First, the gall-bladder has been shown experimentally to contract on its long axis, and wherever longitudinal musculature predominates contractions are seldom visualized as actual peristaltic waves. The urinary bladder, the fundus of the stomach, and generally the lesser curvature of the stomach are examples of this. In a transverse stomach, where the action of the lesser curvature musculature is reinforced by oblique and circular fibers as shown by Forsell, we see peristaltic waves. In the tall individual with a long stomach, where the activity of the lesser curvature depends entirely upon longitudinal musculature, peristalsis is seldom if ever seen under normal conditions. Notwithstanding, no one would deny that the lesser curvature of the stomach, the urinary bladder, and the musculature of the fundus of the stomach contract. It is only natural that contraction of the gall-bladder,

which is under the influence of longitudinal musculature, without obvious peristaltic waves should be the rule.

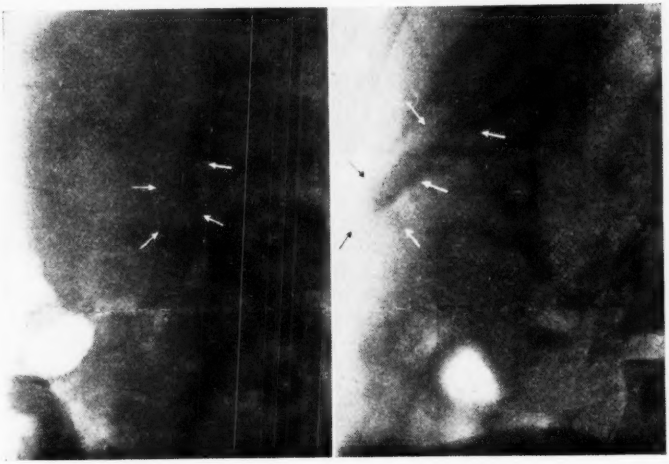
Another reason why the gall-bladder is not visualized more frequently fluoroscopically is due to the fact that two-thirds of it is embedded in the liver in every individual. Further, fluoroscopy is a very tedious process, requiring a great deal of time. However, despite these reasons, Forsell has reported fluoroscopic visualization of the contraction of a gall-bladder filled with dye. He was the first to do so. We, too, once had occasion to note very definite contractions of the gall-bladder in a thin individual fluoroscopically. It is our conviction that if patients were controlled fluoroscopically for one-half to one hour after the ingestion of a fat meal contractions would be seen more often.

Radiographically, contractions have been demonstrated by S. Levine[32] and others. Friedrich and Pflaumer[19] have shown that the gall-bladder may be considerably reduced in size due to hypertonus. It must be remembered, however, that to justify a diagnosis of hypertonus it is necessary, as Herrnheiser[24] points out, to take films not only with the patient on the abdomen (Fig. 110, A) but also in a moderately oblique position (Fig. 110, B). If the reduced size of the gall-bladder is due to hypertonus, as shown in Fig. 110, B, the narrowing of the gall-bladder will persist; if not, the gall-bladder will assume a normal shape in the oblique position. The importance of these observations is that as long as hypertonus of an organ is possible it must be attributed to the effective contraction of the organ's musculature.

Boyden,[10] basing his observations on a series of 50 *x*-rays taken for the purpose of analyzing the reaction of the evacuating mechanism of the human gall-bladder to food, found that before a meal the gall-bladder is either slowly filling or contracting, some of these spontaneous contractions being almost as great as those induced by food. Emptying after a meal of egg yolk and cream is intermittent in character and consists of from one to five contractions. The first phase of contraction is divided into three parts, namely, an initial response of two minutes' duration in which three fourths of the volume of gall-bladder bile is expelled; a second two-minute phase characterized by

filling of the gall-bladder, and a third principal period of discharge when more than half the contents of the gall-bladder are emptied.

Subsequent phases of contraction depend upon how long food is retained in the stomach, repeated ingestions of small amounts of egg yolk into the duodenum inducing but a single phase of contraction.



A B

Fig. 110.—Positions of gall-bladder pictures. A, Patient lying on abdomen. B, Patient in moderately oblique position.

A study of late emptying disclosed marked sex differences, the gall-bladder of the female emptying much faster than that of the male.

Boyden found that drinking water and milk results in an initial filling instead of emptying of the gall-bladder, that is, a reflex inhibition of the gall-bladder; that the injection of air into the duodenum causes a sudden closure of the sphincter and filling of the gall-bladder; that water, yolk of egg, and cream causes a temporary delay in emptying. These are extreme examples of the attempt of the biliary mechanism to produce a

simultaneous closure of the sphincter and relaxation of the gall-bladder.

The smell of food results in the simultaneous relaxation of the sphincter and contraction of the gall-bladder, this type of response producing the greatest flow of bile in the shortest time. The first response after drinking water is a momentary emptying followed by a slow filling, and then by slow emptying, as if there were a hypertonic sphincter which closes after the first stimulus opens it and then gradually relaxes. Here the difficulty is with the sphincter and not with the gall-bladder, as indicated by the speed with which the gall-bladder discharges within the first two minutes when it is merely filling the common duct and not forcing bile into the duodenum. The importance of this sluggish type of response depends upon the possibility that a hypertonic sphincter may, in time, produce a condition of physiologic stasis with calculi formation. Further evidence of dual regulation of the evacuation of bile, Boyden finds, is afforded by the hour-glass gall-bladder in which the gall-bladder continues to contract while the sphincter remains closed.

Boyden and Saunders[11] experimentally demonstrated that the effect of magnesium sulphate in causing the gall-bladder to empty is brought about by the contraction of the gall-bladder and relaxation of the sphincter.

Boyden in his series of cholecystographic films shows that the gall-bladder in the process of emptying first presents a narrowing of the fundus to such an extent, occasionally, that the fundus becomes narrower than the upper part. This could occur only if the gall-bladder actually contracts. The work of Boyden establishes with absolute certainty that the gall-bladder does not empty its contents passively (Figs. 110, 111, 112).

Our own studies, as shown by Figs. 111, 112, also demonstrate that the gall-bladder contracts either in hour-glass formation or as small indentations. It is reasonable to assume that if marked hour-glass contraction or deep indentations are seen they may be due to hyperactivity of the gall-bladder which would occur more often under pathologic than under normal

conditions where the gall-bladder must overcome resistance in order to expel the bile.

Pathology.—Additional proof that gall-bladder musculature plays an active rôle in the emptying of the gall-bladder is evidenced by the fact that in diseases of the biliary tract where the gall-bladder must overcome obstruction for a long period, there is definite hypertrophy of the musculature as an expression of compensatory mechanism exactly as in other abdominal viscera endowed with musculature. Where the obstruction to the common duct is so acute that the gall-bladder cannot participate in

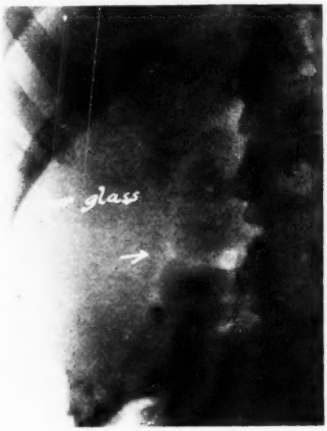


Fig. 111.—Hour-glass contraction of gall-bladder.

overcoming it, dilatation of the intrahepatic ducts transpires, as shown by Judd and Counsellor.[28] This intrahepatic dilatation may be so pronounced as to give rise to what Rous and McMaster term "hydrohepatosis" analogous to hydronephrosis of the kidney caused by obstruction of the ureter or pelvis of the kidney. Where there is chronic obstruction and the gall-bladder cannot aid in overcoming it, hypertrophy of the gall-bladder musculature results and dilatation of the intrahepatic ducts is not marked.

Other Functions of the Gall-bladder.—Aside from the foregoing there are still other functions of the gall-bladder which

are disputed, but which, nevertheless, seem of sufficient importance not to be disregarded. It has been assumed that there is a hormone in the gall-bladder mucosa influencing gastric acidity

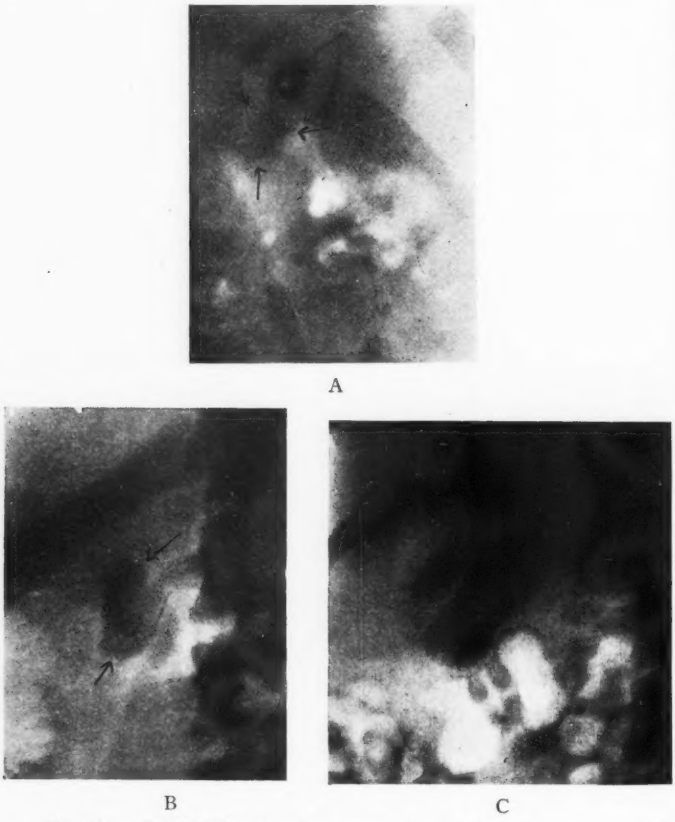


Fig. 112.—Gall-bladder showing contractions during cholecystography: A, Gall-bladder showing three contraction waves. B, Gall-bladder showing contractions and indentation. C, Large contraction wave on gall-bladder.

which may be markedly diminished or even absent in the absence of the gall-bladder. To a certain extent this has clinical significance because it explains why in many cases of cholecystitis,

even following cholecystectomy, there is reduced gastric acidity and even anacidity. Those who argue against this influence of the gall-bladder on gastric acidity base their contention upon the fact that in many cases of gall-bladder disease as well as after cholecystectomy gastric acidity is not altered. Such an argument is invalid, for, although the absorption of bile and the organ's contractility may be disturbed if the organ is diseased, the organ's effect on gastric acidity remains unchanged. Where the gall-bladder is diseased all functions need not be affected. In case of cholecystectomy a compensatory mechanism replaces the influence of the gall-bladder upon gastric acidity.

Another function of the gall-bladder is that the bile it concentrates aids the digestion of fat more efficiently than does liver bile, and in its concentrated form is effective in causing peristalsis of the small intestine and colon. This is significant clinically because after cholecystectomy the motility of the small intestines may be so delayed as to give rise to the so-called intestinal indigestion and the motility of the colon may be so disturbed as to cause obstinate constipation.

CONCLUSIONS

1. Both experimental and clinical data have proved beyond doubt that the gall-bladder is not a useless organ, that its filling and emptying are active processes, and that emptying occurs under active muscular contraction of the organ and relaxation of the sphincter of Oddi, as first suggested by Meltzer.

2. The symptoms often present after cholecystectomy can, in certain cases, be attributed to the fact that the compensatory mechanism of the gall-bladder has not been fully replaced. Further, that where a healthy gall-bladder is removed the symptoms may be even worse than before operation because this compensatory mechanism has not been established.

3. A realization of these facts would limit the tendency of some surgeons to remove the gall-bladder with that indifference with which the appendix is sometimes removed, as a mere prophylactic measure, when the abdomen has been opened for some other abdominal surgical disease.

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PERNICIOUS ANEMIA

DR. C. F. TENNEY: Since the successful treatment of pernicious anemia by the feeding of liver and liver extract and the resulting rapid return to normal blood-counts, with a disappearance of the symptoms that are associated with the disease, it is of great interest, we think, to be able to present in this paper a cured case of pernicious anemia under the old method of treatment. It is likewise of interest to contrast the slow return to normal blood count and disappearance of symptoms in this case to the rapid return to normal in the new method of treatment. Doctor Lintz will present the paper of the evening after which we will have the case presentation and discussion.

DR. JOSEPH LINTZ: So remarkable have been the results of liver therapy in pernicious anemia and so illuminating have been the new found pictures of the pathologic physiology of the disease that interest in this condition has been keenly aroused. We will, therefore, undertake a short summary of our present knowledge.

Pernicious anemia is a symptom-complex affecting the gastro-intestinal, the hematopoietic, and the central nervous systems. It is universally distributed, occurring in all climes. It affects men twice as often as women. It comes on in the middle to latter part of life, the average age of incidence being about forty to fifty. Its onset is insidious and its course, untreated, is chronic with progressive deterioration, stayed now and then by a remission with more or less complete return to health. The first complaints are various and throw no light on the true

causative process so that these cases are frequently incorrectly diagnosed at first.

In over half the cases there are symptoms referable to the gastro-intestinal tract. The mouth and tongue are sore over long periods of time. The tongue shows a smooth shiny mucous membrane, with at times small areas of ulceration. The gastric symptoms embrace anorexia, nausea, and epigastric distress, belching of gas, and vomiting and loss of weight. These symptoms suggest some gastro-intestinal lesion, but roentgenologic examination or postmortem examination shows no gross findings. There is, however, almost invariably an achlorhydria, the significance of which will be discussed later. Diarrhea is a very frequent complaint and occurs in 45 to 60 per cent. of the cases. The diarrhea is persistent and lasts for months or years at a time. It may be quite painless. The loss of weight is not as a rule proportionate to the prostration of the patient.

The effects on the hematopoietic system produce an anemia of a characteristic type, accompanied by progressive weakness. The blood-picture is so typical that the diagnosis may often be made by this alone. There is a marked decrease in the erythrocytes and in the hemoglobin, but the erythrocyte drop is greater than the hemoglobin decline, so that the color index is 1, or greater than 1. The drop in erythrocytes may be very marked. In one case I saw several years ago the initial count checked and rechecked was 700,000. The white blood-cells are diminished in number, but differential counts show that this diminution is at the expense of the granular cells, the lymphocytes being unchanged. This produces a relative lymphocytosis. The platelets, like the granular leukocytes produced in the bone-marrow, are likewise diminished in number. In stained blood films the erythrocytes show considerable variation in size (anisocytosis), but though many small cells are present, the predominating cells are distinctly larger than normal. There is also considerable variation in shape, and many of the cells are deformed. The individual cells vary in their staining, some showing marked central pallor, others staining deeply. There generally are polychromatophilia and basophilic stippling of some of

the cells. Careful search will show nucleated cells, megaloblasts, at some stage of the process. At times these nucleated cells occur in showers. This typical blood-picture may be given by certain other conditions: the anemia of Bothriocephalus latus, the anemia of pregnancy, the anemia of syphilis, the secondary anemias in children, and the anemia of sprue. With these few conditions ruled out, the blood-picture bespeaks pernicious anemia.

In addition, the blood shows evidence of a disturbance of pigment metabolism. The bilirubin is increased moderately but definitely, giving an increased icteric index and an indirect van den Bergh reaction. With this there is a peculiar and distinctive lemon-yellow tint to the skin, which in itself ofttimes suggests the diagnosis of pernicious anemia. The urine may show urobilin. At postmortem there are deposits of iron-bearing pigment in the liver, spleen, and lymph-nodes.

The central nervous system shows evidence of involvement in 80 per cent. of cases through paresthesia, and motor weakness, even in the early cases. There are headache, blurred vision, fainting, and mental symptoms as somnolence, irritability, lack of concentration, etc. In the later cases there may be motor inco-ordination with ataxia of gait and station, loss of tendon reflexes, loss of vibratory sense, loss of bladder control, and loss of motor power due to involvement of posterior and pyramidal tracts—the picture of combined sclerosis. Or there may be accentuation of the lesions in one of these tracts giving a picture of tabes or of spastic paralysis.

Up to the past few years the course of this disease has invariably been fatal. Intermissions occurred apparently spontaneously or might be induced at times by transfusion or splenectomy, only to have a relapse. The free interval might last for many years but if relapse did not occur, the original diagnosis was highly doubtful. The theories to account for the condition were manifold but there were few facts to prove any of them, as it has been impossible to produce pernicious anemia experimentally. The most favored explanation was a toxin evolved in the gastrointestinal tract by some organism which gained entry the more

easily because of the achlorhydria. The toxin then produced anemia by hemolysis of the red cells either directly or through modifying the action of the spleen and directly or indirectly affected the formation of new cells; this same toxin could likewise affect the tracts of the central nervous system. The organisms blamed have run the gamut of bacteriology from anaërobes like Bacillus welchii, through the yeasts like Monilia.

In 1920 Whipple, experimenting with chronic anemia in dogs, found that the most potent foods for the regeneration of hemoglobin were liver and kidney. Based on the work of Whipple, Minot and Murphy essayed the effects of liver feeding in a series of cases of anemia. In those that were of the pernicious type they found a miraculous effect produced by liver. Over 600 cases of pernicious anemia recorded in the literature from varying sources have been treated by feeding liver or an extract of liver, with very uniform results.

There is a rapid change in the sense of well-being of the patient, a disappearance of the lemon-yellow tint of the skin, a sharp rise in the reticulocytes for a period of eight to ten days with a gradual rise in the erythrocytes and hemoglobin. The oral, lingual, gastric, and intestinal symptoms disappear. The paresthesias disappear. The patient is transformed from a complaining invalid to a robust healthy individual. These results in their brilliancy are comparable to the use of insulin in diabetes or of thyroid in myxedema. If liver feeding is discontinued, the same condition previously present will return.

Peabody, corroborating the work of Zadek by obtaining specimens of bone-marrow by puncture, has shown that during a relapse there is a tremendous increase in hematopoietic tissue which crowds and displaces the fat cells, and this hematopoietic tissue contains large numbers of nucleated cells—megaloblasts. In the remission, puncture of the marrow shows normal hematopoietic tissue with plenty of erythrocytes and normal fat cells.

Krumbhaar believes that there is an intestinal noxa somehow associated with achlorhydria and absorbed by the portal system. This hypothetical noxa may in turn in its passage through the spleen stimulate it to excessive hemolysis as well as

damage its normal relation to the hematopoietic function of bone-marrow. In the liver it upsets that organ's hypothetical relation to hematopoiesis, perhaps hindering it in furnishing a necessary ingredient, with the result that inefficient erythrocytes are prematurely ejected or maturation delayed and disturbed, so that in spite of the marrow hyperplasia an insufficient number of inefficient erythrocytes are turned out to be destroyed in excessive numbers. Whipple finds it difficult to reconcile the prompt remission due to liver feeding with a causative agent in the form of an intestinal toxin.

Whipple feels that pernicious anemia is a deficiency disease due to a lack of something necessary for stroma formation. Minot's explanation of the whole phenomenon is that feeding liver supplies some substance which is essential for the maturation of the erythrocytes. Lacking this specific substance the unripe cells are held back in the marrow, few escaping into the circulation. The supply of an adequate amount of the necessary specific substance permits the rapid maturation of many of these crowded unripe forms and the young cells, the reticulocytes, gush forth into the capillaries. As the crowding ceases, the transformation goes on, but more slowly, so that the reticulocyte percentage drops. The specific substance effect has been obtained with fractions of liver prepared by Cohn and his coworkers. While the substance has not been finally isolated, it is felt by Cohn and by West to be not a vitamin, at least such as are known, not a mineral, but a nitrogenous substance of basic property or a polypeptid.

Means and Richardson refer to the work of Castle and Locke who have taken the products of digestion of skeletal muscle in a normal human stomach and fed them to patients with pernicious anemia with a typical response such as is obtained with liver extract. In other words, it would seem that a normal individual obtains from his food some specific nitrogenous fraction or factor which is essential for the completion of the erythrocytic mechanism. In individuals with achlorhydria the interference with the splitting of proteins in time produces a lack of this specific fraction necessary for the maturation of the erythrocytes. Liver

and kidney supply even to this handicapped digestive tract a source of this specific fraction. That achlorhydria generally precedes the pernicious anemia is shown by a number of instances. Christian and Lichty each cite a case where achlorhydria was present twelve years before the pernicious anemia. Ricen cites one of six years' duration of achlorhydria before onset of pernicious anemia.

At this point it is interesting to consider sprue which has many points in common with pernicious anemia. Sprue occurs in most tropical countries, and affects the gastro-intestinal tract and the hematopoietic system. It produces ulceration of tongue and mouth and a copious frothy diarrhea, which is accompanied by emaciation. Some cases have achylia. It presents a blood-picture indistinguishable from pernicious anemia. It may present central nervous symptoms.

In some cases it is impossible to differentiate the two conditions. Christian states that the same patient has been diagnosed as sprue or as pernicious anemia in different clinics, or by the same doctor at different times. He states that sprue cases will develop atrophy of the gastric mucosa and the pernicious anemia picture will come later as a regular sequence. Whether sprue itself is a deficiency disease to begin with, as Elders of Sumatra claims, there certainly develops a deficiency state due to the lack of digestion which enables pernicious anemia to develop. A number of cases were reported by Ashford and one by Richardson and Klumpp which were diagnosed as sprue and which improved markedly with liver extract. The patient treated by Richardson and Klumpp had severe diarrhea intermittently for five years, the first attack coming on suddenly in China. This man developed a severe anemia of pernicious type, but showed moderate gastric acidity. He responded magically to liver extract. The authors concluded that the pernicious anemia was due to a deficiency of a specific substance associated with the gastro-intestinal disturbance. It is likewise interesting to note that liver soup is an old native remedy for sprue in Ceylon and was used by the London School of Tropical Medicine, and is mentioned by Castellani and Chalmers as an effective therapeutic

agent. In fact, the use of liver soup in sprue was one of the incentives for Minot to determine its value for pernicious anemia.

As to the lesions of the central nervous system, the effect of liver has been helpful in clearing up the mental attitude and the paresthesias and motor weakness. In most of the cases with advanced lesions, however, there has been no improvement. Some few cases have shown very definite improvement. The explanation for the lack of change in the central nervous system may lie in the irreversibility of the completed reaction in the white matter of the tracts. Or possibly these changes in the tracts are due to some other protein-product deficiency which is not supplied by the feeding of liver or its extract.

DR. C. F. TENNEY

Case I.—Mr. R. W., white; forty-four years of age; birthplace, Ireland; occupation, hat manufacturer; thirty years in New York City. Admitted to the Fifth Avenue Hospital March 14, 1924.

Family History.—Father died, aged sixty-nine, of arteriosclerosis. Mother died, aged sixty-five, of apoplexy. One brother died of pulmonary tuberculosis. One sister died in Washington Theater collapse. One brother and five sisters living and well. Patient's wife living and well. One daughter has tuberculous pyelitis and is apparently recovering. One daughter has pulmonary tuberculosis and tuberculosis of the larynx and will not recover. No history of heart trouble or cancer in family, but tuberculosis on both sides. Used tobacco and alcohol moderately until 1901, since then none until 1926. Usual diseases of childhood.

Patient had before entering the hospital six transfusions of blood (from 500 to 1000 c.c. at each time) over a period of three years.

Diagnosis.—Cholecystitis with gall-stones with marked secondary anemia. Temperature 97° F ; pulse 64; respiration 20. Present trouble began in 1921 with feeling of weakness and loss of strength and pain in right upper quadrant. Pain was made worse on pressure. Went to St. Mary's Hospital for three

weeks; at end of that time he was discharged worse than when he entered. He changed doctors and was given 10 minims of liquid medicine, t. i. d.; also given two blood transfusions by this doctor—1 pint each time. Health better in 1922 and 1923, but occasional attacks of nausea, some pain in abdomen, and jaundice at times. In January and February 1924 he had four transfusions—1 quart each time. Appetite poor. Weight now 170 pounds; three years ago it was 190 pounds—it goes up and down. Now has deep jaundice over entire body.

Pathological.—March 14, 1924: Blood count: Hgb. 53; R. B. C., 2,950,000; W. B. C., 5000; poly., 53; lym., 41; trans., 4; eos., 2. Anisocytosis, poikilocytosis.

Urinalysis: Sp. grav., 1.021. Reaction, acid. Albumin, a trace. Sugar, negative. Occ. hyl. casts; occ.; W. B. C. occ.; epi.; bile present.

Blood chemistry: Urea N., 12.2; sugar, 84; uric acid, 1.1; CO_2, 45.

March 17, 1924: Stool: no parasites found.

Fragility test: Hemolysis begins at 0.425, is complete at 0.30.

Blood Wassermann: C. A., 1 plus; chol., 4 plus.

Typing for transfusion: Type 4.

x-Ray.—March 17, 1924: Films made of the gall-bladder region in the postero-anterior direction show the lower three ribs, spine, crest of ilium, under surface of the liver, and the lower pole of the right kidney distinctly. Directly in the region of the gall-bladder there is one shadow about the size of a dime and several smaller ones which corresponded in size, shape, and position with gall-stones. There is another more definite shadow in the region of the crest of the ilium which has the appearance of a calcified gland.

Diagnosis.—From a study of these films I believe one is justified in making a positive diagnosis of gall-stones. There is a calcified gland in the right iliac fossa.

3/24/1924: Blood Wassermann, C. A., 1 plus; chol., 4 plus. History of infection denied.

3/25/1924: Blood count: Hgb. 75 per cent.; R. B. C., 3,400,000.

3/25/1924: Seventh transfusion, 500 c.c. whole blood by Dr. Thompson.

3/27/1924: Blood count, Hgb., 83 per cent.; R. B. C., 3,730,000.

3/29/1924: Bile present in stool.

Discharged April 1, 1924. Improved.

Admitted to the Fifth Avenue Hospital again on April 7, 1924, and Dr. Bishop operated. Operation: Cholecystectomy (April 8, 1924). Gall-stones present. No enlargement of spleen.

4/8/1924: Blood count, Hgb. 106 per cent.; R. B. C., 4,570,000. Urine negative for bile.

4/17/1924: Blood count, Hgb. 96 per cent.; R. B. C., 4,980,000.

Discharged on April 25, 1924. Much improved.

After the patient was discharged on April 25, 1924 he presented many of the symptoms of an oncoming cerebral spinal lues. He had a great deal of epigastric distress, cramps in his legs, tingling in his fingers, headaches, and loss of patellar reflexes. Because of former finding of Wassermann with C. A. 1 plus, chol. 4 plus, it was decided that the patient should have some antiluetic treatments. His blood counts remain fairly good throughout the summer and on September 2d he was again admitted to the hospital for lumbar puncture. The spinal fluid was found to be negative, ruling out cerebrospinal lues as the cause of the diminution in his reflexes, pains in legs, and so forth. He did not tolerate the antiluetic treatments very well, but did manage to get up to 24 gtts. of KI. three times a day. The mercury injection he could not tolerate, and because of past jaundice and anemia it was decided best not to give him any of the arsphenamins. Patient was better and worse throughout the fall and winter and again came to the hospital on March 5th, at which time his blood count showed Hgb. 32 per cent.; R. B. C., 1,070,000; and blood Wassermann chol. ant. 1 plus; alcoholic ant. neg. At this time lues was dismissed from mind and treatment for pernicious anemia was started.

Transfusion No. 8: 800 c.c. whole blood by Dr. Thompson 3/5/1925.

3/6/1925: Hgb. 36; R. B. C. 1,520,000.

Blood smear: Poikilocytosis, anisocytosis, polychromaticism. Stippling of R. B. C.; few nucleated R. B. C.

Transfusion No. 9: 540 c.c. whole blood by Dr. Thompson, March 17, 1925.

Blood count March 19, 1925: Hgb. 44 per cent.; R. B. C. 1,900,000.

Discharged March 19, 1925.

Admitted to the Fifth Avenue Hospital March 30, 1925.

Blood count: Hgb. 32; R. B. C. 1,830,000.

Blood smear: Marked anisocytosis, marked poikilocytosis, Stippling of R. B. C.; very occ. nucleated R. B. C.

3/31/1925: Transfusion No. 10, 540 c.c. whole blood by Dr. Thompson.

Discharged April 1, 1925.

4/15/1925: Weight 161½ pounds.

5/13/1925: Weight 154 pounds.

During the few months preceding the admission to the hospital (5/13/1925) there had been a steady enlargement of the spleen, and patient would frequently complain of pain in the region of the spleen. Glossitis and stomatitis were present.

Admitted to the hospital July 7, 1925.

Blood count: Hgb. 24; R. B. C. 1,360,000.

7/8/1925: Fragility test: Hemolysis begins 0.40, complete at 0.35.

Transfusion No. 11 by Dr. Thompson 500 c.c.

7/9/1925: Blood count: Hgb. 27; R. B. C. 1,500,000.

When admitted patient looked pale; pulse weak but regular; temperature 100° F., pulse 96, respiration 22.

After transfusion pulse much stronger. General condition good.

July 14, 1925: Splenectomy operation performed by Dr. Bishop.

July 14, 1925: Transfusion No. 12, 600 c.c. whole blood by Dr. Thompson.

July 18, 1925: Transfusion No. 13, by Dr. Thompson, 600 c.c.

July 18, 1925: Blood count: Hgb. 28; R. B. C. 1,640,000.

Two days following the splenectomy the patient had a chill and symptoms of lobar pneumonia. This was confirmed by the *x*-ray, and patient went through five days of rather critical illness, but fortunately terminated by crisis on the sixth day of his illness.

7/21/1925: Blood count, Hgb. 40 per cent.; R. B. C. 2,200,000.

7/27/1925: Blood count, Hgb. 32 per cent.; R. B. C. 1,900,000.

7/28/1925: Transfusion No. 14 by Dr. Thompson, 500 c.c.

7/30/1925: Blood count, Hgb. 36; R. B. C. 2,420,000.

8/5/1925: During the latter part of this convalescence the patient developed a fissure-in-ano requiring a slight anesthesia and operated by Dr. Bishop.

8/7/1925: Blood count, Hgb. 45; R. B. C. 2,650,000.

8/10/1925: Transfusion No. 15, 600 c.c. whole blood by Dr. Thompson.

8/11/1925: Blood count, Hgb. 50; R. B. C. 3,000,000.

Discharged August 12, 1925.

10/6/1925: Blood count, Hgb. 36; R. B. C. 1,850,000.

Admitted to the hospital October 7, 1925.

10/8/1925: Ewald test: Free HCl, 0; total acidity, 10; occult blood, 0.

10/7/1925: Transfusion No. 16, by Dr. Thompson, 700 c.c. whole blood.

10/8/1925: Blood count, Hgb. 47; R. B. C. 2,550,000.

Discharged October 9, 1925.

Admitted to hospital again 11/11/1925.

11/12/1925: Blood count, Hgb. 32; R. B. C. 2,730,000.

Transfusion No. 17 November 12, 1925.

11/13/1925: Blood count, Hgb. 53; R. B. C. 2,460,000.

During the months of November and December the patient got along very poorly. He looked as if he would probably succumb to his pernicious anemia. He was having a severe glossitis and stomatitis. Taking the diluted hydrochloric acid was difficult for him; he himself thought of a very good scheme for taking it, which was to put it in gelatin globules about the size of castor

oil globules. At this time I was giving him 60-minim doses after meals following up the English method, which was being used at the time.

Discharged November 13, 1925.

Admitted December 14, 1925.

12/14/1925: Blood count, Hgb. 26; R. B. C. 1,990,000.

12/15/1925: Transfusion No. 18, 560 c.c., by Dr. Thompson.

12/16/1925: Blood count, Hgb. 41; R. B. C. 2,000,000. Pain so severe in epigastrium that it was decided to take a G. I. series, which was taken and found to be negative.

12/22/1925: Transfusion No. 19, 520 c.c., by Dr. Thompson.

12/23/1925: Blood count, Hgb. 55; R. B. C. 2,920,000.

Discharged December 23, 1925.

Admitted to hospital January 12, 1926.

Blood count, Hgb. 28; R. B. C. 930,000. Marked anisocytosis, poikilocytosis, nucleated red.

1/12/26: Transfusion No. 20; 500 c.c., by Dr. Thompson.

1/15/26: Blood count, Hgb. 48; R. B. C. 3,100,000.

Discharged January 15, 1926.

Admitted to hospital February 3, 1926.

2/4/26: Transfusion No. 21, 520 c.c., by Dr. Thompson.

2/5/26: Blood count, Hgb. 37; R. B. C. 2,000,000.

Discharged February 6, 1926.

3/26/1926: Blood count, 37; R. B. C. 1,300,000.

4/14/26: Blood count, 53; R. B. C. 1,635,000. Achromia, polychromaticism, basic stippling myoblasts, typical picture of pernicious anemia.

Patient's condition was the same until June 6, 1926, at which time he was advised to move to Long Island, in the country, where he could have the benefit of the fresh air and to try some heliotherapy. At the same time his daughter, who was suffering from a double tuberculous kidney infection, could also take sun baths. He had a generous diet and hydrochloric acid; he had the sunlight and fresh air; he worked around his garden and yard; I saw him occasionally, the patient again returned to the hospital on June 21, 1927—just a year and two weeks from the time of the previous blood count. At which time you can see that

his weight had gone up from 154 to 167 pounds. His Hgb. was 87 per cent.; R. B. C. 3,200,000. What happened during this time to make the improvement in the patient's condition happened after the splenectomy.

It was before the date of liver treatments we know, and from June 21, 1927 the patient steadily improved, as is shown by the blood counts and his general physical condition. The patient went through the remainder of the summer and fall doing light

Mr. R.W. Age 44

Date	Hgb.	R.B.C.	W.B.C.	Poly	Lym.	Eos.	Morphology	Transfusion	Col. Index	Fr
3-25-24	75	3.400.000	7.000	41	59		Anisocytosis Poikilocytosis	500 c.c	1.1	0
3-27-24	83	3.730.000	8.200	62	37	1	Howell-Jolly		1.1	
4- 8-24	106	4.980.000					bodies			
4- 5-25	32	1.070.000	4.000	57	42	1		800 c.c		
3- 6-25	36	1.520.000	3.000	54	42	2	Few nucleated R.B.C.			
3-16-25	38	1.119.000	2.700	46	54		Polychromophilia	540 c.c		
3-17-25										
3-19-25	44	1.900.000	1.800	54	46					
3-20-25	32	1.630.000	2.400	44	56		Achromia Stippling	550 c.c		
3-21-25										
3- 7-25	24	1.360.000	1.000	50	49			500 c.c		
3- 8-25										
3- 9-25	27	1.500.000					4-5-24			
3-14-25							Cholecystectomy	600 c.c		
3-15-25	28	1.640.000	1.000	50	42		3-2-24	600 c.c		
3-21-25	40	2.230.000	4.100	52	40		Lumbar Puncture			
3-27-25	32	1.900.000	4.000	30	62		7-14-25			
3-30-25							Splenectomy	500 c.c		
3-30-25	36	2.420.000					7 - 16-25			
8- 7-25	45	2.600.000	3.500		50		L.L. Lobe Pne.			
8-10-25										
9-11-25							8-5-25	600 c.c		
10- 6-25	50	2.900.000	3.600	16	84		Fissure in Ano			
10- 7-25	56	1.950.000	7.000	46	50	2	1-14-28			
10- 7-25							Lumbago	700 c.c		
10-21-25	50	3.000.000	3.600	16	84					
10-25-25								500 c.c		
11-11-25	52	1.200.000	3.600	20	78					
11-14-25	37	2.230.000								
11-17-25								600 c.c		
12-12-25	52	2.460.000	3.400	26	74					
12-14-25	58	1.990.000	4.600	28	72					
12-16-25								560 c.c		
12-21-25	41	2.001.000	3.200	20	68					
12-23-25	43	1.960.000	4.200	14	86					
12-24-25	55	2.820.000	4.200	40				500 c.c		
1-10-26	70	3.700.000	4.000	46	54					
1-17-26	28	920.000	2.000	15	85		1927 lived in	500 c.c		
1-20-26	48	2.110.000	2.700	22	78		Long Island.			
1-24-26	23	1.400.000	3.500	10	90					
2-21-26								520 c.c		
3-23-26	37	2.000.000	11.500	26	74	1			.8	
4-21-26	70	3.700.000	10.000	42	56		R.B.C. appear			-0
	96	5.700.000	8.000	52	45		normal in size	and shape	Total acidity	6

Fig. 113.

jobs. You will notice the gastric analysis did not show free HCl present, although his blood counts were normal; also at this time his Wassermann was negative in all antigens with a negative Kahn.

Patient was, however, admitted to the hospital on January 14th with a diagnosis of lumbago. This responded to the diathermy treatments and he was discharged in eight days. You will notice that the blood count of March was normal as well as

the following one which was taken this last October, but the gastric analysis done at this time showed no free HCl present. The patient to all intents and purposes is well today, and if he is cured—and I have every reason to believe he is—he is one of the few reported cases who do recover following splenectomy.

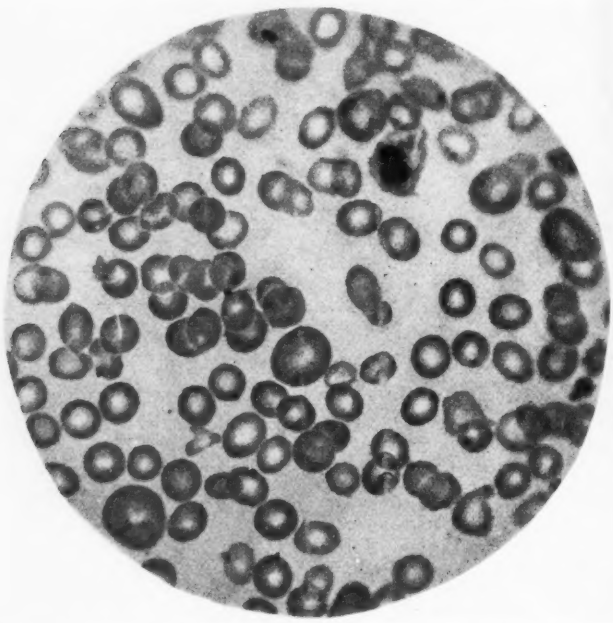

Fig. 114.—Blood smear taken before splenectomy showing anisocytosis and a megaloblast.

At the present time he is somewhat nervous because of the severe illness of his daughter with pulmonary tuberculosis.

We will next take up the pernicious anemia cases which have been treated with liver.

Case II.—Mrs. L. H., aged fifty-four, housewife. Admitted April 17, 1927. Discharged May 5, 1927.

Chief Complaint.—Has weakness and is easily fatigued. Patient stated that for the past eight or nine months she has been progressively weaker. Has lost 10 to 15 pounds in weight and fatigues very easily, but during the past four months she has been having tingling in her fingers and attacks of indigestion.

Physical Examination.—Showed a lemon-yellow tinge to the skin; there was a systolic murmur heard over the entire precordium, but loudest over the aortic area. The reflexes were all active.

Laboratory Findings.—On admission to the hospital: Hgb. 55 per cent.; R. B. C. 1,900,000; W. B. C. 3000; reticulated B. C. 5 per cent., with marked anisocytosis, poikilocytosis.

Icterus index 10; blood Wassermann negative.

Gastric analysis showed no free HCl. Stool was negative for ova or parasites. Urinalysis showed a faint trace of albumin and no casts. This patient was put on liver diet and given hydrochloric acid with meals; after two days there was a marked recession of the lemon-yellow color, and gradually there was steady improvement in Hgb. and R. B. C. as outlined in her chart.

Blood counts:

Date.	Hgb.	R. B. C.	W. B. C.	P. ly.	Lym.	Trans.	Reticulated R. B. C. Per cent.
4/18/1927	55	1,900,000	3000	32	68		
4/19/1927	47	2,100,000	5800	49	48	2	
4/21/1927	38	1,960,000	4000				
4/22/1927	42	1,800,000	3600				
4/25/1927	50	2,400,000	4700	..	..	..	8
4/27/1927	53	2,200,000	5400	..	..	..	7.7
4/29/1927	54	2,500,000	3400	..	..	..	8.5
5/ 2/1927	62	2,800,000	3500	..	..	..	5.5
5/ 4/1927	66	2,900,000	3100	..	..	..	4.5
5/ 5/1927	70	3,200,000	4000	..	..	..	6
5/ 9/1927	69	3,700,000	4300	..	..	..	2.2
5/11/1927	70	3,500,000	4700	..	..	..	2.0
5/13/1927	69	3,200,000	4800	..	..	..	1.5
5/16/1927	78	3,500,000	8600	..	..	..	1.5
5/19/1927	77	3,700,000	8000				
5/21/1927	80	3,800,000	4500				
September	95	5,000,000					

Mr. O. L. T. Age 45

	HGB.	R.B.C.	W.B.C.	POLY.	LYM.	RETICULATED R.B.C.	MORPHOLOGY	COL. IND.	ICT. IND.	FRAG. H.C.L.	Fragility
9-4-28											
9-6-28	28	1.500.000	7.000	67	32		Anisocytosis Poikilocytosis Nucleated R.B.C.	1.0			B 0.45 C 0.3
9-7-28									8		
9-8-28	30	1.500.000				5				0	
9-10-28	32	1.750.000				4.7 Liver begun	Platelets 90.000				
9-13-28	43	1.900.000				6.4					
9-14-28	43	2.300.000				7.					
9-16-28	45	2.800.000				4.5					
9-18-28	48	2.300.000				5.					
9-20-28	66	3.300.000									
9-23-28	70	3.500.000				3.8					
9-27-28	68	3.200.000				3.5					
9-21-28	94	4.500.000				3.					
9- 4-28	94	4.000.000				2.					
9- 7-28											
9- 9-28	94	4.950.000		71						0	
10-22-28	104	6.000.000				2. Liver Ext. 1.6 begun	Patient sent to country.				
11- 5-28								11-5-28	1st Spec.	50	
									Combined	30	
									2nd Spec.	43	
									Combined	35	

	Mrs. L.B.	Age 54									
1-17-27									1.5		
1-19-27	55	1.900.000	3.000	32	68						
1-20-27	47	2.100.000					Anisocytosis Poikilocytosis Slight Poly. Chromophilia			0	B 0.45 C 0.3
1-21-27	38	1.900.000									
4-25-27	36	1.860.000									
4-26-27	42	1.800.000				Liver Begun 6.					
4-27- 27	50	2.450.000				7.96					
4-27- 27	53	2.700.000				8.56					
4-29- 27	54	2.800.000				5.55					
5- 2- 27	62	2.900.000				4.56					
5- 4- 27	66	2.900.000				6.					
5- 5- 27	70	3.200.000				2.84					
5- 9-27	69	2.700.000				2.					
5-11-27	70	3.500.000				1.6					
5-12-27	69	3.200.000				1.					
5-16-27	78	3.800.000									
5-19-27	77	3.700.000									
5-21-27	80	3.800.000								Test Meal 16	
6- 9-28	95	5.000.000									

Fig. 115.

Case III.—Mrs. L. B., aged sixty-one, housewife. Admitted April 5, 1928. Discharged June 7, 1928.

Chief Complaint.—Diarrhea for one and a half years and persistent weakness. Frequent attacks of indigestion.

Past History.—Nothing of especial interest except that she has used Bromo Seltzer for fourteen years in large amounts daily.

Family History.—Essentially negative.

Physical Examination.—There was a marked pallor and a lemon-yellow tinge to the skin.

Laboratory Findings.—On admission to the hospital: Hem. index 1.7; Hgb. 53 per cent.; R. B. C. 1,600,000; W. B. C. 6000; poly. 65; Lym. 33; Monos. 1; Eos. 1. Reticulated cells 2.5 per cent. Marked anisocytosis, poikilocytosis; blood platelets 90,000. Blood Wassermann negative. Icterus index 21. Vanden Bergh negative, direct and indirect. Urea N. 13.8; uric acid 2.3; sugar 85.

Urinalysis showed a faint trace of albumin and occ. Hyl. casts.

Stool was negative for ova or parasites.

Analysis of the stomach contents showed acidity of 15 per cent. for one hour and 21 for one and a half hours.

x-Ray.—Films of the gastro-intestinal tract showed no evidence of cancer or ulcer of the stomach and no evidence of post-pyloric ulcer. Films of the colon were also negative.

Twelve days after admission this patient was started on manganese chlorid, receiving 2 drams of the 1 per cent. solution t. i. d. Within a few days there was a definite improvement in her color; the lemon-yellow tinge disappeared and a slight rise

Date.	Hgb.		R. B. C.	Reticulated R. B. C. Per cent.
4/ 6/1928.....	53		1,600,000	2.5
4/ 7/1928.....	62		2,200,000	
4/ 9/1928.....	50		1,600,000	
4/12/1928.....	53		2,100,000	2.7
4/16/1928.....	62		2,300,000	
4/18/1928 Mang....	60		2,900,000	2.4
4/21/1928.....	60		3,100,000	2.5
4/23/1928.....	66		3,200,000	2.1
4/24/1928	64		3,000,000	2.6
4/25/1928.....	64		3,100,000	2.8
4/26/1928.....	69		3,100,000	2.6
4/27/1928.....	64		3,000,000	2.5
4/28/1928.....	64		3,100,000	2.6
4/30/1928.....	64		3,000,000	
5/ 2/1928.....	64		3,000,000	2.4
5/ 4/1928.....	64		3,000,000	2.3
5/ 7/1928.....	66		3,000,000	2.5
5/14/1928.....	60		2,900,000	
5/16/1928.....	62		2,900,000	
5/18/1928.....	64		2,900,000	
5/21/1928.....	64		3,400,000	
5/23/1928	64		3,000,000	
5/25/1928.....	62	Liver	2,700,000	2.0
5/29/1928.....	58		3,000,000	2.4
5/31/1928.....	62		3,500,000	3.6
6/ 2/1928.....	70		3,500,000	5
6/ 4/1928.....	70		3,800,000	4
6/ 6/1928.....	70		3,800,000	3.6
6/18/1928.....	81		4,150,000	
7/ 3/1928.....	88		3,820,000	
10/27/1928.....	100		6,000,000	
11/ 2/1928.....	..		.....	1

in the Hgb. She was kept for one month on manganese without much progress in Hgb. and R. B. C., but during this time the glossitis and sore mouth were very troublesome and the diarrhea had to be controlled with bismuth. She was also receiving diluted hydrochloric acid with meals. On May 25th she was put on a liver diet, and in a period of six days her Hgb. jumped from 62 to 70 per cent. and the R. B. C. increased a half million. Her general condition, including the stomatitis and diarrhea, also began to improve. On June 18th her Hgb. was 81 per cent. and

trs. 1.8. Age 61

Date	Hgb.	R.B.C.	T.B.C.	Poly.	Lym.	Eos.	Reticulated	Morphology	Col. Ind.	Tot.Ind.	Free H'L
4-4-28	53	1,600,000	6,000	65	33		2.5	Anisocytosis	1.7		0
4-7-28	60	2,200,000	6,000	67	33			Poikilocytosis			
4-9-28	50	1,600,000	6,000	67	31			Nucleated R.B.C.			
4-11-28											10
4-17-28	62	2,100,000					2.7				
4-20-28											18
4-16-28	62	2,000,000					2	Werg. Chloride			
4-21-28	60	2,900,000					2.4	started			12
4-21-28	60	3,100,000					2.6				
4-[illegible]-28	66	3,000,000					2.1				
4-24-28	64	3,000,000					2.6				
4-[illegible]-28	64	3,100,000					2.8				
4-26-28	62	3,100,000					2.67				
4-27-28	64	3,000,000					2.5				
4-28-28	64	3,100,000					2.6				
4-30-28	64	3,000,000									
5- 2-28	64	3,000,000					2.4				
5- 4-28	64	3,000,000					2.3				
5- 7-28	66	3,000,000					2.5				
5-14-28	60	2,900,000									
5-11-28	62	2,900,000						Manw. Chloride			
5-15-28	64	2,900,000		63	34	1.2		stopped			
5-21-28	[illegible]	3,400,000									
5-[illegible]-28	64	3,000,000									
5-30-28	62	2,700,000					2.0	Liver begun			
6-2-28	68	3,000,000					2.4				
6-11-28	67	3,500,000					2.6				
6- 2-28	70	3,500,000					5				
6- 4-28	70	3,800,000					4				
6- 6-28	70	3,800,000					2.5				
6-13-28	81	4,150,000									
7- 3-28	98	5,820,000									
10-27-28	100	6,000,000									
11- 2-28	100	6,500,000					1				0
									Total Acidity		7.5

Fig. 116.

R. B. C. 4,150,000. Her last count, done October 27th, Hgb. 100 per cent.; R. B. C. 6,000,000; W. B. C. 6500; poly. 69; lym. 29; trans. 2, and weighed 120 pounds.

Case IV.—O. S. T., aged forty-five, occupation bookkeeper. Admitted August 4, 1928. Discharged September 12, 1928.

The patient came to the hospital complaining that for the last three months he has been becoming progressively weaker so that he could hardly dress himself or walk a block without

extreme exhaustion. He had lost 20 to 30 pounds in weight during this period.

His past history is rather interesting. He denies any acute illnesses, as well as venereal infection. He has been a heavy drinker for five years, sometimes as much as a quart of whisky daily.

In December, 1927 and January, 1928 he was treated at the Neurological Institute for a psychoneurosis. His symptoms consisted of fear of being alone or of mixing with crowds; general apprehension and nervousness and insomnia. He was advised a course of psycho-analysis, which he could not afford, but apparently his symptoms cleared up, because during his residence here there were no such manifestations.

Physical examination revealed a man weighing 215 pounds, 6 feet 1 inch tall, suggesting the pituitary make-up. He was very pale and his skin was of a lemon-yellow tinge. General body reactions sluggish and he fatigues easily during examination. General physical examination otherwise negative. Tongue is coated, but not much. Knee-jerks are slightly diminished and there are no changes in general sensation.

Laboratory Data.—Blood count:

8/6/1928: Hgb. 28 per cent.; R. B. C 1,500,000; W. B. C. 7000; poly. 67; lym. 32; monos. 1.

8/8/1928: Hgb. 30 per cent.; R. B. C. 1,500,000; W. B. C. 5000; poly. 71; lym. 28; eos. 1. Platelets 90,000; red cells 5 per cent. Definite poikilocytosis and anisocytosis; occasional nucleated R. B. C.

Urea N. 14; sugar 83; urinalysis normal.

Gastric contents: Free HCl. Fasting, 0—one-half hour; 0—one hour; 6—one and a half hours; 14—two hours; total 16; icteric index 8.

Van den Bergh: No reaction direct or indirect.

Fragility test: Hemolysis begins at 4 and is complete at 3.

Phenol sulphonephthalein test 37 per cent. Blood Wassermann negative.

He was put on liver (200 gm. daily) and also given dilute HCl, ℥xx, t. i. d. Within three days his color began to improve,

and after one week the lemon-yellow tinge disappeared. His strength gradually returned, so that at the end of three weeks he was up and around without complaints. In the interim three infected teeth were extracted.

Date.	Hgb.	R. B. C.	Reticulated R. B. C. Per cent.
8/ 6/1928	28	1,500,000	
8/ 8/1928	30	1,500,000	5.0
8/10/1928 liver begun	32	1,750,000	4.7
8/13/1928	43	1,900,000	6.4
8/14/1928	43	2,300,000	7.0
8/16/1928	45	2,200,000	4.5
8/18/1928	48	2,300,000	5.0
8/20/1928	66	3,300,000	
8/23/1928	70	3,500,000	3.8
8/27/1928	68	3,200,000	3.5
8/31/1928	94	4,500,000	3.0
9/ 4/1928	94	4,800,000	2.0
9/ 9/1928	94	4,950,000	2.0
10/22/1928	104	6,000,000	1.6

Patient was sent to Burke's for convalescent care, with instruction to take liver extract, which he did, three doses daily, but he is now eating $\frac{1}{2}$ pound of liver every other day.

Interesting features:

1. History of psychoneurosis immediately preceding recognition of pernicious anemia. Were the psychoneurotic features incidental to pernicious anemia?
2. No glossitis; no complete achylia.
3. Response to liver.
4. Return of HCl.

DR. S. D. JESSUP: In the consideration of this group of pernicious anemia cases, one of them treated by splenectomy and the other by liver diet, it is interesting to note that we start in each case with the characteristic blood-picture of this disease. As the lantern slide picture of the first case Mr. R. W's blood smear shows we have a wide range in size, anisocytosis, distortion, and shape, poikilocytosis and the even deep staining quality of the individual cells showing the high hemoglobin content

which goes with the characteristic high hemoglobin index. In addition we have nucleated red cells, many of them megaloblasts. Other slides from this case showed polychromatophilia, also basic stippling. After the splenectomy there was a gradual loss of this pernicious anemia blood-picture till finally we get the appearance of the red cells closely resembling those of normal blood. In the liver-treated cases the blood-slide study in our laboratory shows the same characteristic changes of pernicious anemia followed after treatment by complete change in the blood-picture. The interesting point to note in this new form of treatment is the fact that the return to normal is rapid in the liver treatment cases when compared with the older forms of treatment such as the use of arsenic, transfusions, or splenectomy.

DISCUSSION

DR. HARLOW BROOKS: I have enjoyed this presentation very much because this is a pertinent subject to all of us, to the specialist as well as to the internist. I do not believe there is any specialty which does not have to call upon a knowledge of the persistent anemias sooner or later. As you know, obstetricians, particularly, have to deal with the anemias of pregnancy which occur not only during pregnancy but particularly after it, a very interesting subject in itself. The pediatrist has a similar problem.

With time, the problems as well as the customs change. The problem of chlorosis is almost as extinct as a dodo at present. I don't believe I have seen a case for several years. Yet when I first started to practice that was one of the commonest things with which we had to deal. A great many errors crept into the account of any disease; one author quoted all too frequently from another. Most of the text-books made the statement regarding chlorosis that it occurred in young malnourished girls particularly. This was not true. Twenty-five years ago I made two analyses of chlorosis, one in Bellevue Hospital Dispensary and one as it occurred in a fashionable school near Fifth Avenue. It occurred as frequently among the exceptionally well-nourished, well-groomed girls as among those of the poorer class. The

patients were well nourished as a rule, well fed, perhaps overweight. The blood-picture was very different from an ordinary secondary anemia. It is important also to recognize that chlorosis continued until adult life and recurred even in old age under extraneous strain and secondary disease in many instances.

This was especially true also in pregnancy, and our idea then was that the anemias of pregnancy were but exacerbations or recurrences of the anemia of chlorosis. I think we were quite wrong in this, as the anemias of pregnancy are quite different in character and form. Chlorosis cases almost without exception responded to ordinary organic or inorganic preparations of iron in a very remarkable way. Five grains of Blandsman three times a day would often bring about an appreciable improvement of the anemia and a very striking improvement in symptoms. Arsenic was employed, with poor effect. My theory is that chlorosis is extinct now not only in the city but in the country as well (it occurred as often in country as in city girls) because of the different type of life today. The ordinary child is kept out of doors a great deal more today than was the custom then. Children are now allowed a great many more liberties in other ways also, some good, some bad. School is not as confining, not so many hours now, and this has had much to do, I believe, with the disappearance of chlorosis. At the time, cases of chlorosis had an almost abnormal taste for chalk, chewing lead pencils, especially the old-fashioned slate pencils, and in my opinion they ate these things to recoup their calcium with considerable benefit just as animals will resort to a salt lick to relieve their anemia.

Chlorosis may not be important now in one way, but it has still a tremendous significance with regard to the study of the genesis of anemia, although the histology and therapeutic treatment are different. There was some factor lacking in the nourishment of these children that is supplied by modern conditions, probably by more outdoor life.

Another form of anemia I would like to speak of, more directly bearing on the subject we are discussing tonight, is radio-active anemia, which is appearing in those who are exposed for a con-

siderable period of time to radium and kindred substances. As you know, the first work done on this subject was in Jersey, and Dr. Martland, pathologist of the Newark City Hospital, was the first to connect radium poison with this form of anemia. He noted that a large number of persons, both men and women, young and old, who worked in a factory having to do with the preparation of watch and clock dials, etc., developed a form of anemia particularly resistant to treatment. The blood-pictures were identical to pernicious anemia, the index was the same, and the blood count and cells fell very rapidly, remaining so for long periods of time, with periods of improvement as in pernicious anemia. These cases showed degenerative red blood-cells, normoblasts, and megaloblasts in large numbers, particularly just prior to the period of improvement, the megaloblasts being very numerous. These cases, however, soon began to come to autopsy and at autopsy it was noted that they showed a very curious condition of the bone-marrow like that in pernicious anemia. In the lower jaw, particularly about the neck of the teeth, there was a necrotic process like that seen in people working with sulphur fumes and like that seen in the smelters where fumes of antimony and arsenic are discharged into the air. These cases of anemia attracted the attention of the health authorities and changes in the smelters have been made so that the fumes have been done away with.

Dr. Martland took a piece of bone from one of these people, strapped it to a photographic plate with adhesive tape, and by his work demonstrated beyond any question that the necrotic process taking place in the bone was due to a radio-active substance identical to that with which the patients were working. The long bones, even the bones of the feet far distant from the point of entry of the radio-active substance, showed the same change. Every bone in the body was more or less radio-active. It is interesting to know that the bone lesions were more prevalent in the girls who pointed the paint brushes by putting them into their mouths, arranging the tips of the brushes with tongue and lips, redipping them into the paint, rearranging the brushes with tongue and lips, and so on. Scrapings of the teeth showed an

abundance of the radio-active substance quite as was to be expected, of course.

There were physicists working in the laboratory who had nothing to do with the painting. They had to do with grinding, mixing, and preparing of the ores. They, too, showed like changes, although not the necrotic changes in the bone, which shows that the substance might have entered the body in other ways, might have entered the skin by handling or by respiration.

If gauze was used like gas masks, it was found that absorption could be done away with. There was a very definite relationship between the degree of anemia, the progress of the case, and the amount of exposure. Those who had been exposed a long time suffered more than those who had been exposed but a short time. Workmen with long vacations, short hours of work, did not develop anemia as completely as the others, and improved. In the progressive cases, however, the course was exactly that of pernicious anemia. Most of them lost their gastric hydrochloric acid and their knee-jerks. We had an absolute simulation of pernicious anemia. The prognosis was identical, for all who developed the disease to a marked degree came finally to an exitus.

I saw 6 cases and definitely pronounced them pernicious anemia. Later, of course, they proved not to be. The cases that came to autopsy also corresponded to pernicious anemia anatomically. The liver, for example, held radio-active substance. This relates very strongly, I believe, to the evolution of pernicious anemia.

May it not be that other substances may also enter the blood or body tissues in a similar way and so cause true pernicious anemia? The question is being studied in a number of places, but nothing definite has come out of it as yet. The idea that we are dealing with an infectious process has been pretty well exploded in pernicious anemia. I doubt if ever we would have accepted this theory had it not evolved during a time when we attributed almost all diseases to infectious processes. In this radio-active situation, we have a disease accompanied by changes in the liver and spleen. In the bone-marrow, one finds radio-

active substances present very definitely, and work with experimental animals shows that the histologic changes in the bone-marrow are precisely like those in the human and those that we have considered as diagnostic of pernicious anemia. Very careful work will have to be done before we can throw away the idea that the invasion of some mineral substance producing changes in the bone-marrow and other organs as in pernicious anemia, may not be the cause of this mysterious malady.

CLINIC OF DR. GEORGE DRAPER

PRESBYTERIAN HOSPITAL

CLINIC FOR THE PRESENTATION OF CONSTITUTIONAL TYPE[1]

Two years ago the attempt was made in the Medical Clinic of Columbia University and the Presbyterian Hospital to demonstrate to the students the relationship of constitution and disease. The exercises designed for this purpose did not follow the plan usually employed to present the clinical picture of this or that malady. Their special object was rather to emphasize the factor which the individual himself, by virtue of his unique constitution, contributes to the etiology of his own illness. Consequently, in order to display, "ipse, the man himself" within the patient, an entirely new method of presentation was adopted.

Before the patient is brought into the clinic room the students are instructed to observe him as though he were not the subject of disease. They are enjoined to make the evaluation of his total individuality their special object. To assist them in this procedure, a series of six blank panels is laid off on the blackboard under the following headings:

HEREDITY; GROWTH AND DEVELOPMENT; MORPHOLOGY; PHYSIOLOGY; PSYCHOLOGY; IMMUNOLOGY

All the information which can be gathered from the patient by direct observation, measurement, or by questions regarding his growth and development, physiologic functions, and psychic pattern is then written upon the board in its appropriate panel. In this way the characters in each panel are correlated and a

[1] The material used in this clinic will appear in Dr. Draper's book entitled "Disease and the Man" to be published by Kegan, Paul, Trench, Trubner & Co., London.

cross-section of the patient is obtained. So far as possible the exercise is carried on without inquiring into symptoms; nor are questions asked that might lead to a discussion of his disease. When the patient's total personality or constitution has been thus laid out upon the blackboard, discussion by the students is invited. As a rule the instructor launches this phase of the clinic by the question:

"Now, in an individual of this sort, exposed to the average pressures of life, where would you look for Achilles' heel, where would the machine first show signs of wear and tear?"

Ordinarily this provokes at once a demand by the students for some information about the patient's special environment, that other essential factor in disease production. But before this aspect of his life is subjected to investigation, the various panels are filled as fully as possible. The objective attitude maintained toward the patient is as much as possible like that which a naturalist in the forest would hold toward an individual of a new and strange species.

There are certain guide posts, however, which are set up by the instructor in his introductory remarks. Reference is made, for example, to the two main functions of any living organism, namely, first, its life of outward relation to environment, and secondly, its inner life of existence and procreation.

The students are particularly urged to remember how subject the human mind is to the confusion arising from the curious relationship that words bear to ideas. As Crookshank has pointed out in his chapter in Ogden and Richards' book entitled "The Meaning of Meaning," the power of words is such that names very quickly become things. As a result, disease, which is purely conceptual, when given a name, may easily take on the fixity of things. We are apt to forget that names are nothing but symbols for ideas. The name of a disease is but the name for a mental construct, built out of the observed phenomena which, for example, arise when a certain bacterium called meningococcus gets into the meningeal spaces of an appropriate human subject. We forget that many people may carry the meningococcus in the pharynx and not develop meningitis.

Our endeavor in this constitutional approach to clinical problems is to bring to bear upon human beings exactly the same kind of objective study as we do upon the meningococcus. We should be able to recognize the different qualities of personality which are found in people who react differently to a given insult. Such differences lie in the depths of the individual constitution. In our eagerness to diagnose the pathologic condition when we are examining a case of heart disease, for example, we are very apt not to notice details of personal appearance. gestures, and emotional tension. Our attention tends to become fixed upon the size and position of the heart and upon the murmurs. And so we are led to forget that it is not the heart, but the whole man who is sick.

INSTRUCTOR: The patient, a man of twenty-seven years whom I am presenting today, is very ill. None of you, I believe, has seen him yet. Please remember, however, that I am not showing you a disease, but a sick man. We shall ask nothing about his symptoms; we shall ask nothing about the history of his disease. We shall try, instead, to find out, as we question him and watch him, what sort of a machine, what kind of a human being he is. We shall try to visualize him as an individual specimen of the race. When you go into a room full of strangers you begin at once to size them up. You wonder what they are thinking of you, and decide what you think of them. Upon what do you base your judgment? How do you distinguish between a Russian and an Italian? Chiefly, doubtless, by the form of his body, his gestures, attitudes, and reactions. How do you tell a ruffian from an idealist? It would be hard to describe your mental processes in making these distinctions, yet you do it easily on the spot. It is possible to refine this distinguishing ability so that you will know the difference between a patient who will get Bright's disease and one who will get meningitis.

The patient this afternoon is a very superior type of individual. He is a college graduate and holds higher degrees than you do. He has very kindly consented to come in and I hope you will think of him as a human being of particular superiority.

(Patient is wheeled in.) Will you all come up closer, please, and meet Mr. ——. Remember, we are not going to talk about what is the matter with the patient. Have a look at him, and then we shall proceed to study his case by a purely objective technic.

INSTRUCTOR: First of all, as a specimen of the human race, in which we are all included, what do you see before you? Is the patient a male or a female?

STUDENTS: Male, and white.

INSTRUCTOR: The first thing we note about any living organism—plant or animal—is its physical appearance. Indeed, if you were walking down the street and saw the building in which we are for the first time, what would be the initial feature to strike you? Its size. Next, its shape. So the first thing we see of anything, really, after we recognize whether it is at rest or in motion, is form. Is it big? Is it small? Is it round? Or is it square? Is it sharp. Or is it dull? We can say what, then, with regard to this man?

STUDENTS: He is long.

INSTRUCTOR: Is he fat or lean?

STUDENTS: Long and thin.

INSTRUCTOR: Let us go into a little more detail. Have you any other observations to make?

STUDENTS: His features are fine.

INSTRUCTOR: Let us take his nose, for example, which carries rather an important index. The nasal breadth is 31 mm., and the nasal height, 51 mm. This gives an index of 62, which places him in the group of the leptorhines, the narrow long nosed people. The opposite extreme, of course, is the broad nose, the index of which may be 100 or more and is found in the negro. We have now this absolute figure as a verification of our original presumption in regard to his race. What do you notice about the head and face?

STUDENTS: Long and narrow.

INSTRUCTOR: The facial index is the length of the face divided by the breadth. In this instance the breadth is 135 and the length 125 mm. which gives an index of 93, a very long face.

Notwithstanding the apparent length of many faces, the breadth is always greater than the length. When you get an index of 93 you have a long narrow facial design which is usually correlated with the long narrow nose. It is not a question of whether these long thin characteristics are good or bad in comparison with the short thick ones. That would be like trying to decide whether a greyhound is better than a mastiff. Each type is adequate to its own particular purpose. So then, in this individual we find a long thin face—proved by actual measurements, and a long thin body. Kretchmer has called these people leptothymic and has found that they frequently are the subjects of schizoid mental disease. Stockard of Cornell terms them lineal types. But, as Hippocrates did, let us speak of them as the long-thins, the opposite of the short-thicks.

Now to proceed a little further. What do you think of the lower jaw in relation to the rest of the face? (To the patient): Without disturbing the relation of the jaws, hold your teeth together as they are now. Can you separate your lips without moving your jaw? Will you all please come closer and observe these jaws. There, you will see what is known as a maxillary prognathism; in other words, a large prominent maxilla extending over the small mandible. What do you notice about his teeth? First of all, the form?

STUDENTS: They are long and narrow.

INSTRUCTOR: What about the relation of the lateral incisors to the central incisors?

STUDENTS: Much narrower.

INSTRUCTOR: The biting edge is what?

STUDENTS: Very sharp.

INSTRUCTOR: The lower teeth are actually and relatively smaller than the upper teeth, so that the whole mandible is small in proportion to the rest of the face. Now, if we further examine the details of this patient's skull we find a gonial angle of 116 degrees. This angle is formed between the posterior border of the ascending ramus and the lower border of the horizontal ramus. It is the one skeletal character which does not vary between the sexes. Notwithstanding the fact that the gonial

angle in the male and female in a given disease group is similar, nevertheless this angle in the patients with one disease may differ widely from that of a sufferer from another disease. The gonial angle of 116 degrees is unusual in this long slender type of person in whom, as a rule, an angle of 125 degrees would be found. But there is no absolutism in nature; mixed forms are now universally found. As Dr. Barker remarked not long ago while discussing a problem in genetics, "the human being today is actually a polyhybrid heterozygous bastard."

Let us take his eyes now. What do you notice about them?

STUDENT: They are deep set.

INSTRUCTOR: I will hold my finger at a point two or three feet away from them. What do you perceive now?

STUDENT: There is ptosis on the right.

INSTRUCTOR: Are you justified in that statement? It may be an example of the danger of an ill chosen word. Is ptosis the best, or is there something else you might say?

STUDENT: Unequal openings.

INSTRUCTOR: We find a palpebral index of 31 on the right and 44 on the left; that is the ratio between the length and breadth of the fissure. You don't need instruments to show such a discrepancy. But measurements are valuable when you are studying a series. The palpebral openings in this man, then, are irregular. But there is some question in your minds about the eye set. Someone said something about prominence. That doesn't coincide with the earlier statement, deep set. As a matter of fact, these eyes may be classified as either or both. The rather large overhanging supra-orbital region gives the impression that the eyes are deep set; but in respect of the orbital margin they are slightly prominent.

Looking at his hair, do you notice anything?

STUDENT: It is abundant, rather coarse and dry; there is a difference in color—brown with a reddish cast. It has a crinkle, too.

INSTRUCTOR (To the patient): Is there any red hair in your family?

PATIENT: Yes.

INSTRUCTOR: It is actually astonishing how often, when you find this slight glint of red or copper color in a patient's hair, there turns out to be someone in his family who has frankly red hair. Don't forget that red hair is a variant in every race. Blond and brunette are the classic hair colors in human beings. You know the number of remarks that prevail about red-headed people. Such individuals are not only variants in respect of their hair color, but also in respect of a great many other things. They are supposed to have quick tempers; they react differently in disease from the average. When you see people with red hair watch them for different kinds of reactions, a little off the usual. Red hair at once makes a patient interesting. When you find a variation in one department of the personality it should immediately awaken you to the possibility of variations in other departments. The red haired ones' resistance to infectious disease may be different from that of the average blond or brunette of the region. Or the variations may manifest themselves in physiologic differences. Such an individual may not be able to digest easily the things another can. Or, the variant tendency may manifest itself in unusual psychologic reactions. In other words, the red haired person is apt to be a little different.

When we come to study the patient's trunk we find that the A. P. D. is 205 mm., indicating a flat type of chest. The range for the general population is 190 to 220 mm. and the deepest chests are found in subjects of acromegaly, pernicious anemia, and gall-bladder disease. The flatness of this patient's chest is further emphasized by the A. P. D. Chest L. index of 57. (Gall-bladder 66.8.) Going on now to the matter of the ratio of sitting height to lower extremities, we find it as 8 is to 10, a definitely eunuchoidal character. To sum up then, we can say that this individual is unusually tall and slender with flat thorax and narrow subcostal angle. He is an example of what general type?

STUDENT: The linear or asthenic.

INSTRUCTOR: With this information about the patient's chassis, let us see if we can discover something relating to his growth and development. He is very tall, 6 feet, 2 inches.

(To the patient): Were you full grown when you were twelve years of age?

PATIENT: No.

INSTRUCTOR: When did you attain your present height?

PATIENT: At fifteen.

INSTRUCTOR (To the students): Suppose you compare him to other human beings at fifteen, what would you say from the standpoint of height?

STUDENT: Way ahead of them.

INSTRUCTOR (To the patient): Were you a long, thin bean pole?

PATIENT: I certainly was.

INSTRUCTOR (To the students): What produces extreme long bone growth?

STUDENT: Pituitary.

INSTRUCTOR: Why should the pituitary run away with the body? What is the experience of the religious sect of the Skopsi in middle Europe which practices pre-adolescent castration? The castrated individuals outgrow their fellows. You know that the effect of the gonads upon the pituitary is very decided. There appears to be a checking influence exerted by the gonads upon the pituitary's long bone growth stimulating effect. All the long-legged boys have had a strong pituitary growth before the normal checking influence of the gonads commenced. No one grows evenly in all departments. The growth and development of an individual is like a platoon of raw recruits marching down a field. The unpracticed line bellies and sags most irregularly. But the platoon is marching on toward maturity all the time, and when the drilling period is over the finished line is usually fairly straight; all the dents (retardations) and bulges (precocities) have been ironed out. When human beings reach twenty-five, they are pretty well finished products. But if there are serious, uncompensated retardations, the whole adult is handicapped. In this case there is evidence, not only from the patient's statement but in the circumstance of his height and trunk extremity ratio, that before puberty he grew very rapidly. In other words, the awakening of the growth checking factor

supplied by gonad influence in this individual was a little retarded. But there may be another factor which also helps to determine this man's size and form, something behind the endocrine. There may be a family characteristic, an inheritance pattern. (To the patient): Is your father a tall man?

PATIENT: Six feet, 1 inch.

INSTRUCTOR: How about your mother?

PATIENT: Five feet, 9 inches.

INSTRUCTOR: And your brother?

PATIENT: My own brother is 6 feet, 3 inches, my half brother 6 feet, 1 inch.

INSTRUCTOR: A little light begins to come through, doesn't it? Your sisters?

PATIENT: One is rather short, the other medium.

INSTRUCTOR: There is evidently a factor for length displayed in the inheritance pattern of the male offspring. You can see that in this way we begin to get a clearer impression of the quality of this individual. Let us now make a few investigations in the immunity panel. How about the so-called childhood diseases: mumps, chickenpox, etc?

PATIENT: Whooping-cough at approximately ten, no scarlet fever, typhoid between eleven and twelve, mumps at sixteen, chickenpox at eighteen, measles at twenty-three, and pneumonia at twenty-six.

INSTRUCTOR (To the students): Is there anything unusual about the age at which these diseases developed?

STUDENT: Childhood diseases very late.

INSTRUCTOR: In this individual, then, what does this peculiar situation in the immunity panel suggest in association with the phenomena already disclosed in the growth process?

STUDENT: Whatever the maturing factor, it was delayed.

INSTRUCTOR: Yes, in two or three departments of the total organism. What effect from this do you suppose one might find in the psychic panel? When we come to this aspect of personality we must remember that we are dealing with two phases that have but scant correlation with each other. Indeed, they are usually in conflict; the intellect on the one hand and emotions

on the other. All that goes to form feeling is quite one story; thinking is another. Long before we begin to think, both chronologically and in the presence of given situations, we feel. In fact, all our reactions to life are determined in the first instance by feeling; the manner in which we behave is a secondary consideration. We are not primarily thinking, but feeling organisms. The more highly developed the individual, the more complicated and intense become these psychologic processes. Suppose you took a three-year-old infant and put it at the wheel of a rapidly moving automobile. What would he feel?

STUDENT: Confusion and fear.

INSTRUCTOR: Let us ask the patient, who says that at the age of fifteen he was a long thin bean pole, how he compared in athletic contests with husky thick-set boys of similar age.

PATIENT: Up till fifteen, very poorly.

INSTRUCTOR: Did this circumstance give you a sense of inadequacy, a feeling that your chances of getting on in the world were small?

PATIENT: Yes, I had a great sense of perplexity and insecurity.

INSTRUCTOR: What did you do, if anything, to help yourself?

PATIENT: I decided to get strong and set to work studying and exercising. I worked my way through school, including college.

INSTRUCTOR: It is interesting to observe that in this case the reaction to the sense of perplexity and insecurity was an energetic and positive one. He reached out, as it were, and engaged actively with the objects and affairs of life about him. He studied hard, exercised his body, and, in addition, worked his own way through school and college.

Did this process make you feel more secure?

PATIENT: Yes indeed, as long as I was busy I didn't have those vague feelings of indefinable, impending disaster.

INSTRUCTOR: This response, gentlemen, is a striking reiteration of the old story that to engage actively with the affairs of the palpable universe is one way in which to escape the fearsome effects of any dragons that may be lurking in the mind's sub-

conscious caverns. To grasp firmly an object in immediate reality does much to offset the vague unrest which springs from an habitual sense of insecurity. This method of gaining assurance is used more successfully by the type of person whom Jung has called extraverted, than by the other, or introverted one.

(To the patient): Have there been periods in your life, after you became a fully mature individual, in which a situation arose giving rise again to those same feelings of insecurity; situations in which there was premonition of impending disaster, or apprehension?

PATIENT: There was a change in my ideas of religion during my college studies; and a more critical and suspicious observation of people.

INSTRUCTOR: Do you think this was associated with an analogus feeling of insecurity within yourself?

PATIENT: I think so.

(The patient is now wheeled out of the room.)

INSTRUCTOR (To the students): One has to be very careful in eliciting a description of feeling, because the conscious mind is sometimes quite incapable of recognizing or even admitting the existence of a feeling, particularly one concerned with the problem of self-preservation. Fear, apprehension, or the sense of inferiority is not readily admitted by most men. Yet emotional hypersensitiveness is quite obvious in this patient. During the first two or three interviews with him, after he entered the ward, red blotches came out on the skin of his neck and face and his hands were moist and cold most of the time. What would such disturbances in cutaneous circulation indicate? What is the usual interpretation of altered circulation of the skin?

STUDENT: Vasomotor disturbance.

INSTRUCTOR: Ordinarily brought about by what?

STUDENT: Emotional upsets.

INSTRUCTOR: In the case of this man hypersensitiveness, chiefly fear, wondering whether people are critical about him; what they think about him; for he is acutely concerned with the problem of whether he can survive physically and spiritually. He reminds one of the soldiers who went over the top during the

war. They were much more worried about losing their reputation for courage than their lives. That the fear emotion exerted its effect upon the apparatus equipped with smooth muscle was shown by the many cases of sudden diarrhea which developed just before the hour of attack. It is difficult to discuss and demonstrate the whole content of the psychic panel, but we are able to gain some idea of his personality by watching a patient as we talk with him, by noting whether he responded emotionally, whether anxiety, fear or timidity, is present, whether his answers are slow and deliberate or quick and jerky. What did you notice about this patient's answers?

STUDENT: They were quick and terse.

INSTRUCTOR: How about the duration of his sentences and the sustaining of his ideas?

STUDENT: Not very long. Everything was said quickly.

INSTRUCTOR: Pretty intense?

STUDENT: Yes.

INSTRUCTOR: Now then, we are beginning to get a cross-section of this individual. First of all, morphologically, he is of the long-thin type, displays certain evidences of delay in maturing, and possesses an extremely hypersensitive, quick-reacting, and rapidly exhaustible psychic pattern.

He did his best to co-operate with us in this interview, but it was difficult for him. He looked uneasy most of the time. His responses were quick and made in a little constrained voice. There were, likewise, swift, fleeting changes of his facial muscles, and quick, apprehensive gestures and glances. He was easily fatigued. If you will pause to think of the way in which any animal defends itself in its environment you will recall that its defense depends upon muscular contraction. It is either fight or flight. The relationship of life to environment is carried on by the voluntary or skeletal muscles. We change our relationship to a menacing environment voluntarily. If, on the other hand, you are dealing with the inner life of existence, you are concerned with entirely different factors over which there is no conscious control whatsoever. The self-preserving and perpetuating mechanisms are equipped with non-striated muscles—

pulmonary muscle, cardiovascular muscle, gastro-intestinal muscle, genito-urinary muscle—over none of which is there will direction. All the vital processes upon which the individual must depend for his very existence are entirely beyond conscious control. This whole involuntary mechanism, however, responds to the emotions. We cannot augment the heart rate or contract the arteries by willing, nor can we slow and dilate them by willing. But the functions of heart and vessels can be modified for us by the three fold mechanism of our emotions, the endocrine glands, and the sympathetic nervous system. The same principle holds for the other smooth muscle systems. It is common knowledge that violent diarrhea may follow an emotional disturbance.

But similar emotional experiences provoke quite different physiologic responses in different people.

Now, with this in mind, what do you think of this man? What sort of human machine is he? Would you put him in the class of those to whom relationship to environment is the chief concern of the total personality, or in the class of those to whom the activities of the inner existence are the more vital?

STUDENT: I would say in the class of those mostly engaged in the task of relationship to environment.

INSTRUCTOR: Quite clearly the events, objects, and personalities in this patient's environment provoke intense and rapid responses in the smooth muscle zone. You have only to look at him and he gets red. You have only to touch him and his hands burst out in perspiration, his forehead becomes moist. It is apparent from the response of his involuntary systems to any pressure of life that he is at the mercy of every slightest change in his palpable environment, or to the interpretation he puts upon its psychologic significance. So far it would appear that in this patient the fear component was the predominant factor of his emotional maladjustment. Yet the sex factor cannot be overlooked. It is, however, quite impossible adequately to develop this phase of the psychologic panel before a group of people. But there are several points of interest in respect of this patient's sex life which should be presented to you. In

the first place he discussed the whole subject without embarrassment and displayed a thoroughly adult attitude toward it. He began to masturbate at ten years of age and continued till he was fifteen. There seems to have been no especial sense of guilt provoked by this experience. The urge apparently ended spontaneously and at sixteen he entered what was apparently a natural, and for a period of three years, satisfactory sex relationship with a girl of his own age. This attachment was terminated by his departure from San Francisco following the earthquake and fire. During the next five years he had one or two transient experiences with women. But he stated emphatically that these were unimportant, chiefly because he was so occupied with his efforts to support and educate himself. It was also evident from his attitude toward the first episode that he had felt a deep affection for the girl and had been seriously depressed following his removal. At the end of the five-year period during which he had been working at the University and struggling with the changes in his religious philosophy, he married one of the students with whom he had been associated in academic interests. This marriage so far has been successful.

The patient's dream life also is of interest in its bearing on the distribution of the fear and sex factors in his subconscious processes. In general he has always dreamed a good deal. As a child he had nightmares and walked in his sleep. He says that fear phantasies preponderate and that sex appears but little in the dreams.

One dream in particular is most suggestive because of the association which it awakened. You may recall that the patient had a younger brother who was everything both physically and mentally which the patient himself desired to be. He cherished this brother and looked after him as a father would a son. A few nights ago the patient dreamed that he and this brother were back in their childhood, playing together. Suddenly the dreamer had a sure presentiment of his brother's impending death. He said nothing to the brother about this, but was filled with a sense of combined grief and apprehension. Then the dream moved on to a display of the horrible details of his

brother's death and he awoke calling out, "Mother, Mother, I'm dying."

Thus it would seem that in the dream the patient identifies himself with his much admired brother. The "grief and fear" at the prospect of the brother's death is the unconscious fear of his own. It was interesting that almost at once after telling the dream the patient said: "Now that's funny, but it reminds me that in giving you my father's history I neglected to tell you that he has a cancer of the mouth." A few moments later he admitted that for some time he had been secretly fearing that his own symptoms might be due to a beginning cancer.

We should not be satisfied to let our evaluation of this phenotype rest, however, with the statement that his emotional-endocrine-sympathetic mechanism is maladjusted. We should attempt to determine which of the vital systems equipped with the smooth muscle is least capable of withstanding the pressure of life. We might ask him, for example:

(Patient is brought in again.)

(To the patient): Do you tire more easily from physical exertion, or mental effort, or following some emotional stress?

PATIENT: Usually much more after getting nervous and apprehensive. At school I had no trouble in athletics, but I remember trembling with excitement and my heart pounding violently when I held up my hand to answer a question in the class room, although I knew the answer well. Then I felt exhausted and weak in the pit of my stomach.

INSTRUCTOR: This reply serves to turn our attention, for the moment at least, upon those bodily systems wherein physiologic change swiftly follows an emotional stimulus. The changed functional state is indicated in this patient by two purely subjective sensations, pounding of the heart and weakness in the pit of the stomach. But these reactions appeared at an early age and he has grown accustomed to them, anticipates them. As John Hunter remarked that his life was in the hands of any rascal who roused his temper, so this man inevitably reacts to the fear of criticism or failure with the feelings he has described.

At this point it may be of value to seek for any factors in

the heredity or environment of this phenotype which may have contributed to the production of his asthenic form, his hypersensitiveness, and to the inadequate qualities of particular tissues or systems wherein may lie his Achilles' heel, his locus minoris resistentiæ. (To the patient): Will you tell us something about your parents and brothers and sisters?

PATIENT: Both my father and my mother had some Indian blood in their veins, but they never talked much about that. My father was an excessively nervous, high-strung person, very irritable, and domineering. He was irregular in his business success. Sometimes we would be on easy street, and then, before you knew it, wondering where the next meal would come from. My brother, who was a year and a half younger than I, was huskier, and for awhile, before I started to grow fast, at about fourteen, was taller than I was. He could do everything better than I could, too.

INSTRUCTOR: Were your sisters strong and healthy?

PATIENT: Well, yes, that is, they were my half sisters, daughters of my father by a former marriage.

INSTRUCTOR: Were they both healthy?

PATIENT: Yes.

INSTRUCTOR: Are both living?

PATIENT: Yes, that is, one is.

INSTRUCTOR: How about the other, what did she die of?

PATIENT: Well, she committed suicide, shot herself.

INSTRUCTOR: How old were you when this happened?

PATIENT: About thirteen or fourteen.

INSTRUCTOR (interrupting): So that this shock came while you were still small, just before you started to grow?

PATIENT: Yes, and shortly my father lost everything in the San Francisco earthquake and fire. After that we moved away to a little place he had back in the country. Father and mother ran this as a sort of boarding house or hotel and I went to the country school. When I was about nineteen I moved again to a town about 30 miles away where I could go to a better school. I wanted to become a writer, but my father said that was absurd and that I should stay and help him run the hotel.

So I worked my way and when I was twenty my father got angry and wrote me saying he was through with me if I insisted on going to college. I remember that on reading his letter the same sinking feeling in the pit of my stomach came on.

INSTRUCTOR (interrupting—to students): Now, at that time was that well localized subjective sensation which he described primarily emotional or gastric?

STUDENT: Emotional.

INSTRUCTOR: It was clearly an emotion akin to fear, aroused by the sudden sense of isolation from the family, a situation of insecurity; he was facing the world, led by his ambition on the one hand, and doubtful of his ability to succeed on the other. His history does not describe an atmosphere which was calculated to establish a sense of security and self-sufficiency in a delicate boy.

(To the students): Which emotion, then, has been more or less continuously active in this patient from boyhood?

STUDENT: Fear.

(Patient is wheeled out.)

INSTRUCTOR: There seems little doubt about it. On a deep-rooted basis of insecurity, fear has been the paramount influence in this patient's psychic content. Let me call your attention to the writings of Cannon and of Crile on the physiologic effects of fear. It is, of course, now common knowledge that the adrenal gland is intimately associated with the sympathetic nervous system in the physiologic effects of fear; and that the circulatory system and gastro-intestinal system especially reflect this emotion. But on the basis of the facts so far elicited, I doubt if it is possible to come closer to the probable site of this patient's lesion than to say that one might expect it either in the cardio-vascular or gastro-intestinal systems.

STUDENT: Why look for a lesion? Why not consider it normal of him to show these reactions?

INSTRUCTOR: That is a very interesting question. Don't you think, though, that "normal" is a confusing word? If you must define normal I suppose you would say that it is functioning effectively without discomfort. From the standpoint of an

individual whose perceptive powers and reaction capacity are comparatively adequate, your question is very well taken. This man's symptoms, however, are so severe that they prevent his working. Further than that, they threaten his life. Have you any idea as to what the lesion is?

STUDENT: Hyperthyroidism.

STUDENT: It might be gastric ulcer.

INSTRUCTOR: Anything else? Any dissension from these?

STUDENT: Sympathicotonia.

INSTRUCTOR: That is simply an overemphasis of the qualities of the personality we are speaking about. As a matter of fact, the man has an immense gastric ulcer, lying half inside the pylorus and half outside. He has had very severe hemorrhages. The extraordinary feature of his gastric attacks, however, is that they bear no relation to the taking of food, but are associated with something else. In every instance these have followed a situation in which his individuality, his idealistic ego, has been threatened. Here is a list of them:

First Attack.—At nineteen years of age when he ceased to attend the high school in the city and began going to the school up in the country. This necessitated a breaking up of an attachment which he had formed for a girl and removed him from the contacts and opportunities which his excellent intellectual endowment demanded and which were provided by the city school.

Second Attack.—This was a very severe one and occurred between the ages of twenty and twenty-one. It happened in the period of transition between high school and college in which the break with his father came and which resulted in the removal of the parental protectorate.

Third Attack.—At the age of twenty-two he moved to the University town and was meeting great difficulties in finding means of support. He was doing odd jobs of a very menial character. Furthermore, he worried about his mother's nervous breakdown at the time of her menopause. At that time, also, he was entering into perplexing spiritual and religious controversies. In these he broke away from his paternal teachings and found himself launched in a new field of religious thinking. He seemed

to be progressing out of the security of his traditional beliefs and was goaded into unknown regions of thought. He developed a great fear of insanity which was augmented by the memory of his half-sister's suicide.

Fourth Attack.—At the age of twenty-seven, as a result of a controversy with the faculty of Stanford University in which he attacked them in such a way as to make the loss of his job probable and imminent, he began to see that he might have to leave. His first ideas of migrating to the east began to develop.

Fifth Attack.—In Montana, en route to the east in a motor car with his wife and a friend, he became conscious of the fact that he was permanently severing his early connections, and that he was moving into new and strange territory. He began to develop very severe pains in his stomach and had such a bad attack that he was laid up three weeks with it.

Sixth Attack.—This one (the one that brought him into the hospital) ensued upon his finding it so impossible for him, a stranger, to secure a footing in New York that he was forced to move once more, this time to Stamford, a small neighboring city.

It is of unusual interest to note that the forerunner of each of these attacks was the perilous experience of moving from a known and fairly secure situation into an unknown one.

Here, then, is an individual of asthenic build, with morphologic details common to a large group of people who have had gastric ulcer. Psychologically he is hypersensitive and shows qualities of swift response, rapidly discharged energy, and scant endurance. His growth and development were slower than usual so that early in life he was exposed to feelings of insecurity with its attendant fears. Furthermore, the tissues of the father's central nervous system were of a nature which permitted distinctly inadequate reactions, and the epithelium of the entrance of the father's gastro-intestinal tract has shown pathologic potentialities. From the side of this patient's environment we can pick out the sister's suicide, the younger brother's physical prowess, the earthquake's destructive effect on the home security, and finally the break with the father, as examples of fear producing menaces. When such a phenotype receives upon the

psychic mechanism blows of such magnitude from the environment it is almost inevitable that a gastric ulcer will develop.

The routine clinical study recorded on the patient's chart has clearly demonstrated the presence of an ulcer.

Now, so far as treatment is concerned, there are two things to be dealt with. The ulcer is there and must be managed with the care that any local lesion of the sort demands. Rest, appropriate diet, and, if necessary later on, a gastro-enterostomy. But in view of what we have learned about the patient's emotional traumata and consequent maladjustments, these therapeutic maneuvers are insufficient. We cannot escape the duty of attempting by some psychologic technic to develop in the patient insight into his subsconscious conflicts. The more we see of this type of human being, the more does the seriously destructive influence of the fear emotion upon them become apparent. Some individuals respond best to simple direct suggestion, some to re-education, and some to psycho-analysis. The selection of the technic appropriate to a given case is a matter of importance. The object of the psychotherapy is to reduce or eliminate the destructive fears.

CLINIC OF DR. A. BENSON CANNON

BABIES' HOSPITAL

DERMATOLOGIC CONDITIONS AS SEEN IN CHILDREN

WHILE most of the dermatologic conditions found in adults may occasionally be seen in infants and young children, there are certain affections of the skin—infantile eczema, impetiginous eczema, prurigo mitis, and the various nevi or developmental abnormalities—which are usually associated with infancy, either on account of their greater frequency in this period of life, or because their appearance is noted at this age. In this paper we shall concern ourselves with the various types of eczema and closely allied conditions.

Of the many dermatoses seen in infancy J. M. H. Macleod in "Diseases of the Skin," published in 1926, states that 25 per cent. belong to the eczema group; and we find that of the total general admissions to the out-patient department of the Babies' Hospital in 1926 numbering 4258, 115 or about 3 per cent. were afflicted with some form of eczema. In our work we endeavor to classify the various types of eczema, where possible, according to cause, such as infantile, seborrheic, staphylococcic, streptococcic, and mycotic, believing that only in this way we can hope to obtain the best therapeutic results.

Infantile Eczema.—We have found that in every 100 cases of eczema about 39 were of the infantile type. This variety usually occurs between the third week and sixth month of life, most often before the third month. It almost invariably begins on the cheeks as a bilateral, symmetrical, bright red, raw oozing, crusted, and pruritic condition, gradually spreading over the face, neck, body, and extremities as a diffuse catarrhal dermatitis.

Occasionally the diagnosis of infantile eczema is rendered difficult on account of a secondary impetiginous infection: in such cases one is lead to suspect the true nature of the disease by the history of the occurrence of the initial lesion on the cheeks in early infancy, and also by the persistence and character of the eruption after the cure of the impetigo.

Sir Norman Walker, "Introduction to Dermatology," 8th edition, 1925, and others, while advising careful investigation of the feeding and the correction of all possible errors in diet,

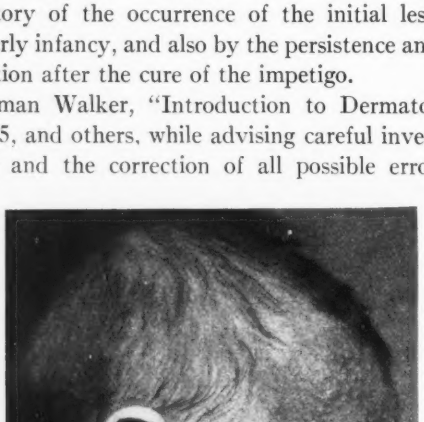

Fig. 117.—Infantile eczema. Case from Vanderbilt Clinic, New York.

maintain that the most reasonable explanation of the cause of infantile eczema lies in a slight exaggeration of the ordinary high susceptibility of the infant's skin to external irritants, such as septic discharges, feces, urine, vomitus, and irritating soaps. He further points out that the investigations of Dr. Arthur Hall have shown that no constant relationship to an internal disorder exists. On the other hand Dr. J. A. Fordyce in "The Common Skin Diseases" published by Paul B. Hoeber in 1925, states that where eczema in infants appeared on the cheeks and

spread over the face and other parts of the body, excessive feeding with sugar and fats, or a sensitization to some food product may be the etiologic factor. My observations coincide with the views expressed by the latter and while I believe that some cases may be due to focal infection in the tonsils, sinuses, etc., the chief cause is metabolic in the majority of instances. Whatever the etiology, it is a notable fact that infantile eczema is more prevalent and is seen in its most severe form among the poorer classes where babies are badly cared for and are reared in unsanitary conditions.

The treatment consists in the removal of foci of infection where present, correction of diet, and local therapy; often a combination of these is most ideal. I have seen many cases of infantile eczema in which the examination for focal infections, stool cultures, and the various skin tests were done, and the diet changed many times without any improvement in the skin eruption, and yet these same cases cleared up entirely or almost so, with cornstarch baths, soap, and water, and an ointment of zinc oxid or Lassar's paste containing from 10 to 25 per cent. of naftalan and from 6 to 24 per cent. of crude coal-tar, oil of cade, or liquor carbonis detergens, this ointment alternating with a triple strength calomine liniment, containing 5 to 10 per cent. ichthyol and an equal percentage of liquor carboneol, wiping off the excess and dusting with a bland talcum powder. One of the most important features of the treatment is the bandaging of medication on the affected parts and preventing the child from scratching himself, the latter to be effected by the use of some mechanical appliance. Cases of generalized eczema of a severe character which have resisted all of the previously mentioned forms of treatment often clear up almost magically with *x*-ray, alpine light, or alternating doses of alpine and *x*-ray. While we have been very successful in freeing the patient from the immediate attack of infantile eczema, we have not been able in most instances to prevent recurrences, but fortunately the subsequent outbreaks are usually of a much milder type than the first and are more easily controlled provided that the treatment is resumed immediately. As a rule the prognosis is good,

the disease, barring secondary infection, having very little influence on the general health, and a majority of the children outgrow the condition.

"Candy" Eczema.—In children we frequently observe circumscribed dry, finely scaly, mildly erythematous, round or oval-shaped patches of eczema occurring on the sides of the face and simulating a seborrheic dermatitis, but without the characteristic location and oily scales of the latter. This condition is almost invariably associated with a high carbohydrate intake and is often spoken of as "candy" eczema. Limitation of sugar with applications of some bland ointment suffices to clear up the condition.

Prurigo mitis, a chronic dry, scaly, finely papular, intensely pruritic condition of the skin, occurring in early childhood, is sometimes confused or classified with infantile eczema or with lichen urticatus, the latter a type of papular urticaria. Prurigo mitis usually begins on the extensor surfaces of the extremities as small pin-head to millet-seed sized, grayish papules followed by scaling, and a thickening of the skin. Ultimately the eruption becomes universal, with enlargement of the superficial glands, especially the inguinal. It is usually seen in pale, undernourished children, somewhat below par physically, and is worse in winter months. While the cause has not been established it is thought to be due to a metabolic disturbance, possibly protein sensitization. The condition becomes greatly improved by scrubbing with soap and water, using bran or cornstarch baths, and the application of 4 to 6 per cent. sulphur ointment; 2 per cent. beta-naphthol or 4 to 10 per cent. tar ointment are also useful. Prurigo mitis seldom entirely disappears; it is a chronic inflammatory condition of the skin, continuing until adult life or longer, many of the cases dying from some intercurrent infection.

Seborrheic eczema occurs on the scalp of infants as a dry, scaling affection, gradually spreading over the forehead, ears, neck, and face, and appears on the body as circumscribed, erythematous dry, or slightly oily, pruritic patches, varying in size from a twenty-five cent piece to a silver dollar or larger. It is

usually easily cured by frequent bathing with soap and water and the application of a 5 to 10 per cent. ammoniated mercury ointment, or an ointment containing a 4 to 6 per cent. sulphur alone or in combination with 1 to 3 per cent. salicylic acid. This medication may be alternated with triple strength calomine lotion containing from 5 to 10 per cent. liquor carbonis detergens. In extensive or resistant cases, generalized alpine light in addition to the other remedies usually suffices to clear up the condition (Fig. 118).

Fig. 118.—Seborrheic dermatitis beginning on the scalp.

Pyogenic Eczema.—Another affection, pyogenic eczema, begins on the scalp of infants, usually beneath the vernix caseosa, as a moist, crusted, and oozing condition, often spreading over the face, neck, ears, and body as itching, circumscribed, erythematous crusted patches, frequently with a mucopurulent discharge and associated with enlargement of the cervical glands. The treatment of this condition is very similar to that of seborrheic dermatitis, consisting of the application of antiseptic preparations, such as ammoniated mercury, sulphur, or salicylic acid ointments. In pyogenic eczema as in all other crusting, scaling, or thickened conditions of the skin, the free use of soap

and water is indicated; this to be followed by the application of 2 to 5 per cent. of salicylic acid in castor oil. In severe cases, potassium permanganate, bichlorid of mercury, or boric acid baths are very useful.

We always bear in mind that these eczematized conditions of the skin are apt to become infected with streptococci, either in the form of an erysipelas, abscessed glands. or septicemia. I have recently seen a child aged seven months, suffering

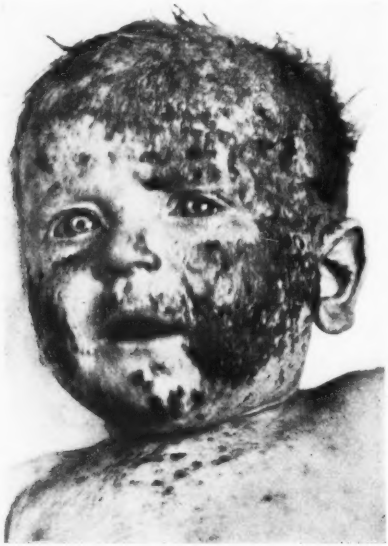

Fig. 119.—Pyogenic eczema beginning beneath the milk crust. Same case as Fig. 120.

from a severe, crusted pyodermic infection of the scalp, face, neck, and body, of three months' duration, who developed abscessed glands of the neck, followed by erysipelas which gradually spread over the entire cutaneous surface, the child dying seventeen days later.

Infectious Eczematoid Dermatitis.—In children we not infrequently see a dermatitis similar to pyogenic eczema beginning on the scalp and neck and due to staphylococcic infection sec-

ondary to pediculosis capitis. This condition usually spreads over the face and at times even over the body. It may also be secondary to some focus of infection such as a discharging ear or an abscess where the pus is allowed to remain on the skin surface, thus producing a secondary dermatitis with a true

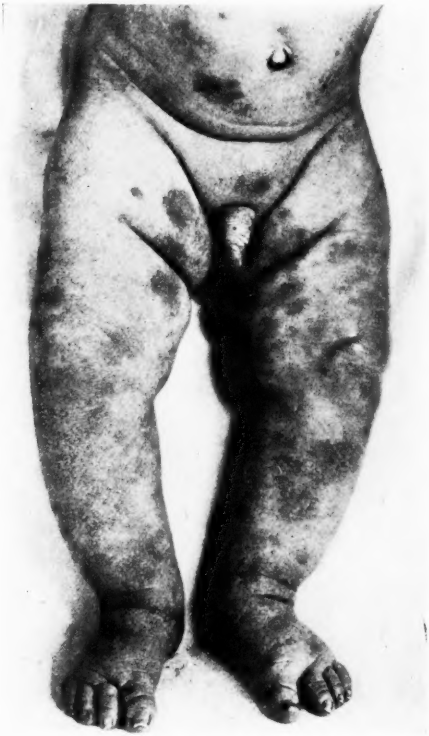

Fig. 120.—Pyogenic eczema. Same case as Fig. 119.

sensitization of the skin and a generalized eruption. This condition was first described by Dr. M. F. Engman in "American Medicine," 1902, 1903, vol. 4, p. 769, and later by Dr. J. A. Fordyce in "Journal of Cutaneous Diseases," 1911, p. 129, as infectious eczematoid dermatitis.

Follicular Impetigo.—We must also mention in this connection a follicular impetigo, an infection due to the staphylococcus, usually occurring on the buttocks, presenting small pin-head to pea-sized follicular, papular and pustular lesions, and sometimes gradually spreading over the entire cutaneous surface. Some of the lesions may coalesce forming hazel-nut sized furuncles. The condition not infrequently occurs in infants physically below par and ends in death from sepsis or intercurrent disease. The treatment consists of antiseptic baths of boric acid, potassium permanganate, bichlorid, and alcohol sponges, 2 to 4 per cent.

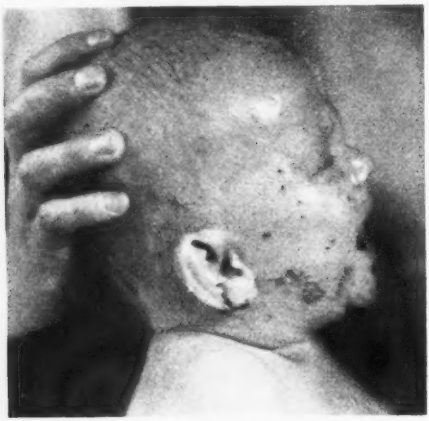

Fig. 121.—Infectious eczematized dermatitis secondary to a discharging ear. From the service of Professor Wilcox, Babies' Hospital, New York.

sulphur in Lassar's paste, one-half unit of *x*-ray, repeated in two weeks, and autogenous or stock vaccines. I recall one extensive case in which all of the above remedies had successively failed and the child got entirely well following a few injections of colloidal manganese (Fig. 122).

Contagious impetigo, a streptococcic infection of the skin, is most commonly seen in young children. It occurs on the exposed surfaces, face, and extremities, as small, erythematous, pruritic, macular, dime- to half-dollar-sized areas, the center of the lesion rapidly becoming vesicular or bullous. The serum

of the vesicles quickly becomes cloudy, the walls rupture with the formation of a thick yellow colored, waxy crust, so superficial in character as to give the appearance of an artefact.

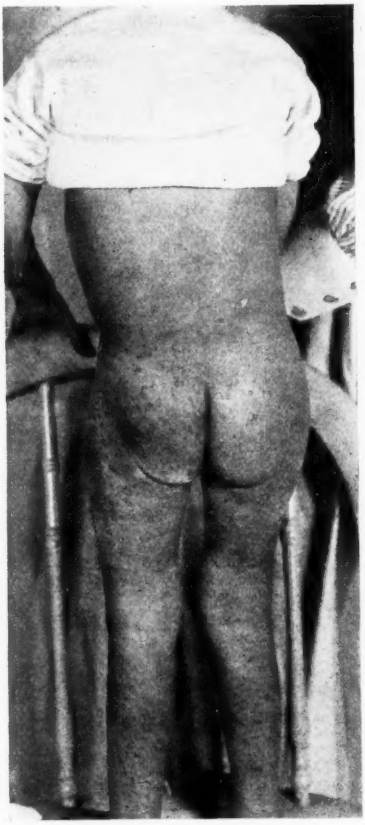

Fig. 122.—Follicular and pustular impetigo. Case from City Hospital, New York.

Sometimes the lesions become circinate in outline with clear centers and spread at the margins, resembling circinate ringworm. Impetigo is both auto-inoculable and contagious and may become generalized. If the lesions ulcerate the condition is

designated ecthyma. We have a specific for impetigo and ecthyma in ammoniated mercury ointment, 5 to 15 per cent., or sulphur ointment, 4 to 6 per cent., used in conjunction with soap and water (Fig. 123).

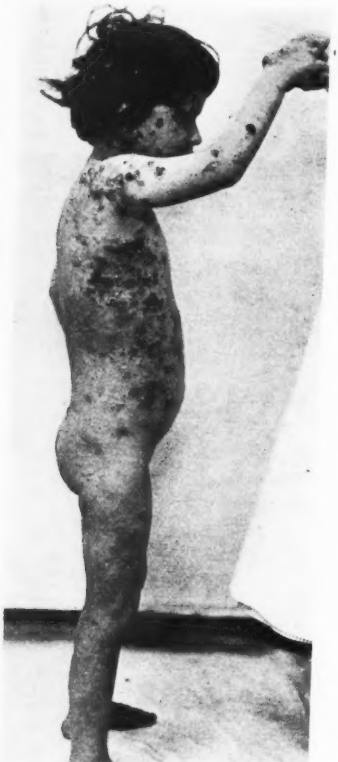

Fig. 123.—Contagious impetigo showing numerous bullæ with crusting. Case from City Hospital, New York.

Ritter's Disease.—In the newborn we occasionally see a contagious impetigo which not infrequently becomes universal, manifesting itself as a moist, scaly affection of the skin, so-

called Ritter's disease. This type is also due to the streptococcus and is *oftentimes* fatal, the infant dying with a streptococcic septicemia or from sepsis. The condition is usually seen in maternity hospitals, and is thought in many instances to have been caused by puerperal sepsis in the mother. There was a serious outbreak of this infection in one of the local hospitals a number of years ago which ended in several fatalities—H. J. Schwartz Bulletin of the Lying-in Hospital, June, 1908, p. 6, "An Epidemic of Pemphigus Neonatorum." On the other hand, an epidemic occurred on the maternity service of one of the hospitals in the vicinity of New York about one year ago, some fifteen infants becoming diseased, but without the loss of a single patient. The treatment given them was the same as that prescribed for the other forms of impetigo contagiosa, combined with prompt isolation of the affected babies and individual nursing. As soon as the eruption had disappeared the babies were removed to a sterilized room for a period of observation before being discharged.

Mycotic Eczema.—Occasionally we see in infants on that part of the skin covered by the diaper a sharply demarcated erythema with an area of denuded epithelium in the center and a dry scaly margin; this we designate mycotic eczema. The patient may develop similar though smaller patches on other parts of the body, or vesicular lesions on the palms and soles, and dystrophy of the nails. This variety of eczema is often confused with the diaper rash, or so-called "Jacques dermatitis." The differential point, however, is the dry scaly margin and the parched appearance of the central portion of the lesion together with the demonstration of spores and mycelia in scales taken from the lesion. Usually there is no difficulty in curing these cases with potassium permanganate baths, ammoniated mercury, or sulphur ointment, or the application of 2 per cent. iodin or iocamfen, the latter being neutralized after three to five minutes with lotio alba compound. Where the skin is excessively tender and excoriated the baths may be used alone or followed by dusting with boric acid powder.

Lichen chronica simplex, a type of eczema usually beginning

in childhod and often recurring at intervals until the patient's twentieth or twenty-fifth year, appears usually on the flexor surfaces, in front of the elbows and wrists, behind the knees, on the neck, scalp, and on the face at the margin of the hair. The areas are intensely itchy, of a brownish erythematous color, dry, finely scaly, and papular, some being excoriated from scratching and resulting in a considerable thickening and

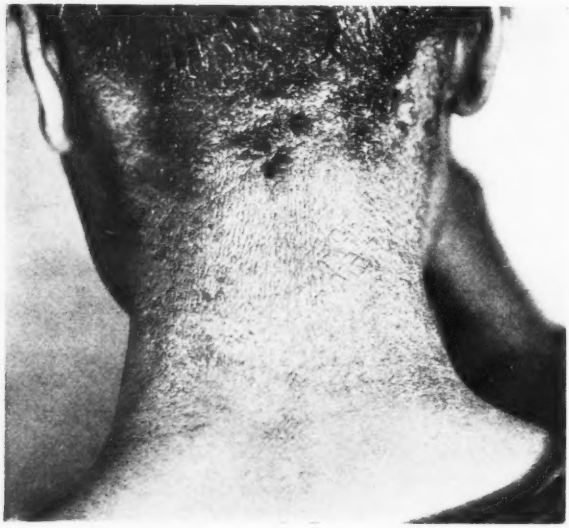

Fig. 124.—Lichen chronica simplex in a young woman. Case from Vanderbilt Clinic, New York.

leathery-like condition of the skin with exaggeration of the lines of cleavage (Fig. 124).

In the severer types of the trouble the upper part of the chest and the entire flexor surfaces of the upper and lower extremities may be involved. The general health is usually unaffected except for irritability and nervousness incidental to the intense itching and the accompanying loss of sleep. The majority of these cases are thought to be the result of a sensitization of the skin to some external irritant, such as dander,

fur, feathers, hair, or orris root. Treatment, while often very effective in clearing up the annoyance, does not prevent recurrences. In the milder localized types, therapy consists in painting the areas with a solution of chrysarobin, chloroform, and tincture of benzoin compound, afterward dusting on some bland talcum, or painting with crude coal-tar, liquor carboneol, or liquor carbonis detergens. A solution of ichthyol may be used in the same way often with excellent results. Generalized alpine light combined with concentrated light on the affected areas is also a useful remedy, especially when used with the above medication. In protracted and resistant cases one-half unit of *x*-ray given every two weeks, usually in combination with local remedies, will serve to relieve the itching and clear up the condition miraculously, the relief sometimes lasting for months or a few years at a time.

Being able to distinguish between the several types of eczema and recognizing the indications for suitable treatment of each frequently enables one to predict with some degree of certainty the results which can be obtained in the individual case. While we are unable to effect a lasting cure in all children suffering from true infantile eczema, we can always alleviate the condition for a longer or shorter period. The infectious seborrheic and mycotic eczemas can be promptly, satisfactorily, and permanently cured by using the ordinary antiseptic and antiparasitic remedies.

CLINIC OF DR. THOMAS J. HARRIS

NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL

THE SOCIAL ASPECTS OF PROGRESSIVE DEAFNESS (OTOSCLEROSIS)

THE term "otosclerosis" was first used by Toynbee in the year 1857 (in his catalog of 1149 specimens) to describe an ankylosis of the stapes in the oval window which he had found in 126 of the specimens.

This term was used for many years to denote such an obstruction to the sound waves whether of a membranous or a bony nature. But it was not until 1865 that it was demonstrated by Bezold microscopically and physically that the loss of hearing for low tones was the result of such rigidity in the oval window.

For an affection of this kind, due as he believed to a primary involvement of the labyrinthine capsule, Politzer employed the term "otosclerosis." In the last thirty-five years, extensive research has been made by numerous observers, including Politzer and Manasse, Siebermann in Basle, and Gray in Glasgow, into the nature of the disease, especially in regard to its pathology.

One of its characteristic features was supposed to be that the disease is inherited. A considerable degree of agreement in regard to the pathology has been arrived at but down to the present time no treatment leading to a cure has been discovered.

During the last few years otologists have come to the conclusion that in order to treat the affection successfully it is necessary accurately to determine the cause or causes, and, today, in various parts of the world, extensive investigations are being carried on in this direction. More and more otologists have come to believe that the term "otosclerosis" is a misnomer and should

be abandoned. In its place various terms have been suggested, including that of otitis insidiosa by Bryant, but generally otosclerosis is thought of as the form of progressive deafness that is inherited.

Much, in medicine as in other branches of science, is accepted upon tradition or upon the authority of others. So with the rôle that heredity plays in progressive deafness. That it is found in a considerable number of cases there can be no question. Fraser[1] states that in at least 50 per cent. of cases a history of deafness in the family can be obtained. Shambaugh is of the opinion that no case is true otosclerosis in which there is not an hereditary history.

For the last two years, in connection with a study of progressive deafness, we have been inquiring carefully into the family history of every case presenting itself. In doing this we have been assisted by a representative of the American Eugenic Society. While we are not in a position to give exact results at the present time, it may be stated with positiveness that among the patients who have been referred to us, representing all or most of the cases of progressive deafness presenting themselves during three days of the week at one of our largest New York hospitals, the number of those with a clear history of familial deafness is far below 50 per cent.

It is not an infrequent experience to be told by a patient that a parent or grandparent was deaf, only to find upon inquiry that the deafness began at an advanced age or as the result of suppurative disease or injury. This, in our opinion, will account for the prevailing opinion that inheritance is a constant factor. If our contention is correct, it naturally improves the prognosis for those suffering from the disease.

On the other hand, when a clear familial history is obtainable, an additional element is present to make the prognosis for recovery bad and to enhance the probability of the progress of the deafness. The following is the most outstanding "tree" of cases of inherited deafness which we have met.

This represents four generations beginning with a great grandmother, in the second generation four children, in the third

generation eight children, and in the fourth generation two children. It will be noted that in the third generation there is a union of two deaf persons with the result of two children one of whom, a girl age fourteen, is already beginning to be deaf. We have had an opportunity to study the majority of these people carefully. In most of those who have reached adult life the deafness has advanced to a pronounced degree.

Using this chart as a text we wish to allude briefly to the important social aspects involved in familial deafness and the responsibility thrown upon the specialist in charge. For the most part it has to do with young women at the marriageable age. Usually they will consult the specialist only after they have

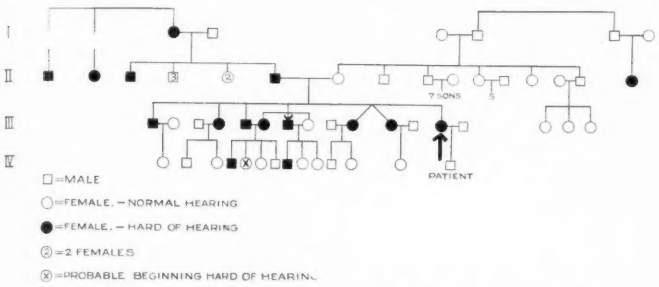

Fig. 125.—Chart of four generations of familial deafness.

begun to suffer from impaired hearing. Occasionally, where the family history is very clear, their attention will be directed to it while they are still possessed of normal hearing. What advice shall be given them in regard to marriage and particularly in regard to motherhood?

Authorities differ greatly in regard to the frequency of otosclerosis. Fraser estimates that one case in every 200 suffers this disease. Whatever the exact figures are, the physician sooner or later will be confronted with the necessity of giving the proper advice. To tell a young woman that she should not marry or that, if she marries, she should not have children is advice not to be given except upon the most mature and careful consideration.

As a general observation, it may be said that when a deaf

person without a history of familial deafness marries a person with normal hearing, the risk, so far as deafness in the offspring is concerned, is comparatively small.

If, on the other hand, the husband, in addition to the wife, is suffering from progressive deafness, the risk of the offspring becoming deaf is exceedingly great. The duty of the physician in such a case is plain. It is to tell the wife the probability that any children she may have will be deaf, is large, and to advise her against having children.

Still more clear is his duty if it is a question of the marriage of one deaf person with another who is deaf where a familial history exists. Here motherhood, because of its effect upon the hearing of both the mother and the child, is particularly to be condemned. Cases of this nature are rare and will not often call for advice.

Quite different is the situation when it has to do with young women who, although without any familial history, are already partly deaf and who are about to marry or are already married. The result of our study as well as of the studies of most other observers is that pregnancy is very apt to have a bad effect upon the hearing of the deafened woman. We have out of 60 odd cases of progressive deafness definite records of fourteen women where the history was one of no or comparatively slight deafness until the first or subsequent pregnancies, when, almost in a moment, the hearing became seriously affected. Encouragement is lacking in such cases that in time the hearing may be recovered. Usually it remains permanently impaired. The reason for this has not been definitely determined. More and more an endocrine unbalance is being regarded by investigators as the chief or at least as one of the chief factors in bringing this about.

The following are the histories in brief of the 14 cases referred to above.

Case I.—G. T., age thirty-three years, married, deafness in the left ear following the birth of a child six and one-half years ago. Dyspituitarism. Deafness is progressive and does not respond to treatment.

Case II.—R. C., age thirty-three years, three children: five, fourteen, and seventeen. Deafness began after birth of third child. A hypothyroid case.

Case III.—E. N., forty-three years, first noticed deafness after birth of first child. No change after birth of second child. Marked hypertension.

Case IV.—A. G., age twenty-eight years, four children, deafness began with birth of third child. Hypothyroidism.

Case V.—Mrs. R., one of a family of twelve, all suffering from hereditary deafness. Patient and two sisters (Cases VI and VII) became deaf following birth of children.

Case VIII.—E. Z., deafness from third pregnancy. Endocrine unbalance.

Case IX.—I. W., deafness followed birth of first child.

Case X.—S. D., age twenty-five years, deafness occurred after birth of child.

Case XI.—Mrs. W., age twenty-four years, deafness began before marriage, increasing with birth of child.

Case XII.—M. Z., deafness began with birth of seventh child.

Case XIII.—K. F., age twenty-four years, deaf as child but much worse after birth of child.

Case XIV.—Mrs. S., married, six years' deafness following birth of child.

It will be noted that in most of these cases there was a history of deafness beginning in childhood and before marriage, but brought in evidence for the first time on the birth of a child.

An equally important group is that where no deafness existed prior to motherhood and where the deafness began at that time. A possible explanation for these, of course, is that the deafness had not been recognized. A still more probable explanation is that there was present in all of them a latent endocrine unbalance which required only the exciting factor of pregnancy to make it active instead of passive.

At a recent meeting of the Austrian Otologic Society the subject was discussed at length. Some of the leaders of the profession there were pronounced in their view that in such cases motherhood must not be allowed. They were prepared

to go as far as to assert that when pregnancy does take place an interruption is the proper course to be carried out.

Conrad Stein[2] took part in the discussion and contributed an exhaustive paper. He reported 23 cases of women in whom the deafness began or was made worse by pregnancy. A high degree of loss of function followed the first pregnancy in 3 cases, in 4 cases the second, in 3 cases the fourth, in 4 cases the fifth, and in 1 case the seventh pregnancy. He quoted numerous German authorities as having also observed this fact. Various explanations for this have been advanced. Neumann thinks it due to the lowering of bone resistance, Cornett to auto-intoxication, Otto Mayer to an increased growth of otosclerotic areas in the pregnant woman. Mayer states that what are called puerperal osteophytes are observed in other bones. Alexander thinks the bone changes to be of a congenital nature. Stein's opinion is that there is a constitutional diminishing of the hearing due to developmental anomalies in the labyrinthine capsule, there being a predisposition to otosclerosis on the one hand and, on the other, to atrophy of the nervous apparatus. In Stein's opinion anyone of the following five causes makes the danger to hearing from pregnancy pronounced:

1. If there is already disease of one ear or if the increase in deafness in both ears sets in at the beginning of pregnancy, especially with labyrinthine symptoms.
2. If there is a history of heredity.
3. If there are signs of pronounced irritability of the vegetative, *i. e.*, of the cardio- and the vaso-vegetative nervous system.
4. If there are signs of endocrine unbalance; and
5. If there are symptoms of toxemia.

In such cases he advises the interruption of the pregnancy.

Burger[3] reports a case of pregnancy where on account of deafness the pregnancy had been interrupted. This case was discussed at the Dutch Medical Society, where Struycker and Quix did not approve. Burger has reported another case in favor of his contention where, on account of religious views, the pregnancy was not interrupted and the patient became much worse.

Frey[4] favors interrupting the first pregnancy in such cases. The decision in regard to what to do in a second pregnancy should depend upon the result to the hearing of the first.

At the Vienna meeting mentioned above a committee was appointed to petition the Austrian Parliament to repeal the present law governing the interruption of pregnancy.

No one realizes better than the otologist the serious significance of all that is bound up in this question. We are dealing, however, not with a theory, but with a condition. The family tree given above is sufficient to show the evil consequences of marriage in cases of inherited history when children are the result. Despite all that we know at present, we are unable to do anything with certainty to prevent the advance of the deafness in the children of the fourth generation in this family. One child, indeed, aged only ten, whose hearing is still acute, shows beginning changes with the audiometer.

The otologist especially will be called upon constantly to advise his patients on this subject. He must be prepared to have his advice disregarded. Love of children and the homing instinct are too strong to be set aside lightly. There can be, however, no question of what his duty is under the circumstances. Fortunately the number of cases where two persons with familial histories of deafness wish to marry is exceedingly small. For women giving a history of familial deafness who desire to marry, the advice of the physician—the family physician even more than the specialist—that they may marry but should not have children ought to carry much weight.

Far more real and pressing is the much larger group of women—already deaf, although without familial history—who are married or about to marry. Our case reports and those of Dr. Stein show how prone such women are to a marked increase of their deafness following childbirth. In such cases the physician has his gravest responsibility. Recognizing fully what it entails, it is our deliberate judgment that he should carefully point out to his patient the risk she assumes in having children, and should advise her, if as the result of his examination he has discovered an endocrine unbalance or a focal infection present,

that she should not become pregnant or that, if she does, pregnancy should be interrupted. In such cases whatever may be brought against the practice on other grounds, this would seem to be a proper and just reason for its exercise.

No man will consciously allow the wife whom he loves to become, on account of her deafness, a burden to herself and to others. The danger that this will happen if she becomes a mother is so great that it cannot be disregarded. Intelligent, conscientious advice from the family physician and the specialist will go a long way to prevent its occurrence.

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CLINIC OF DR. JESSE G. M. BULLOWA

From the Medical Service, Harlem Hospital (Dr. Lewis K. Neff, Director), and the Littauer Pneumonia Research Fund of New York University

SERUM TREATMENT OF THE PNEUMOCOCCUS PNEUMONIAS

Specific therapy of the pneumococcus pneumonias depends upon accurate recognition of the type of the invading organism and on prompt application of suitable potent serum. In view of possible errors and the need for haste in the application of the remedy, one may be compelled to use the serums for the most prevalent types, pending more careful study.

During the past season one of our co-workers, Mr. A. B. Sabin, has developed and applied on our service a very useful improvement in the method of typing. It has the following advantages: it reveals the type sooner and often more conclusively than the older methods; at the same time it furnishes a permanent record which may be checked. It requires much less material and paraphernalia and much less time for its performance. It has been used in upward of 250 typings without apparent deviation from the type given by the older methods when the same material is used.

The test is performed in the following manner: 2 c.c. of sputum (thinned with saline if need be) is injected into the peritoneal cavity of a mouse. At the end of three or four hours a glass capillary pipet is inserted through the skin and some of the peritoneal exudate is withdrawn. At this time the sputum has usually been digested by the peritoneum and the organisms have multiplied sufficiently so that typing may be proceeded

with. In Type III cases there may be sufficient organisms at the end of two hours. A glass slide has been divided into four parts and on each a minute drop of the peritoneal exudate is expelled. The first is thoroughly mixed with an equal sized drop of normal saline solution by means of a platinum loop. A one-tenth dilution of each of Type I, Type II, and Type III of the diagnostic serum is then mixed with the drop of peritoneal exudate in the appropriate section. They are stirred with the platinum loop so as to be thoroughly mixed and spread so that the slide dries rapidly in the air. The preparation is next fixed in the flame and stained in dilute alcohol fuchsin. Under the microscope the appearance of the agglutinated organisms is characteristic. The illustration (Fig. 126) depicts Type II organisms (*a*) as they appear in the control or normal saline section or as they appear when mixed with heterologous serum and (*b*) as they appear when mixed with the Type II serum. You will notice that in the control slide (*a*) the pneumococci are scattered over the field with a clear capsule about them; in the slide (*b*) in which the diagnostic serum has been added you will find them clustered together with a deeper staining, smaller capsule.

We have controlled our results taken at this time with the results obtained by washing out the peritoneal cavity and typing in accord with the standard procedure in upward of 250 cases. We have also taken as a control a culture from the heart's blood of the dead mouse and typed it after it has been grown in broth.

Wherever organisms are present in sufficient number, this method can be quickly applied. It is directly applied to a broth culture from the patient, or, in cases of meningitis, to the cerebrospinal fluid, or to the peritoneal exudate of a patient with peritonitis. If there is no agglutination in Type I, Type II, and Type III, additional drops may be taken and mixed with dilutions of the typing serums for the other types described by our co-workers, Cooper, Edwards, and Rosenstein, of the Littauer Pneumonia Fund, and recently published in the Journal of Experimental Medicine (March, 1929). At present we are typing for

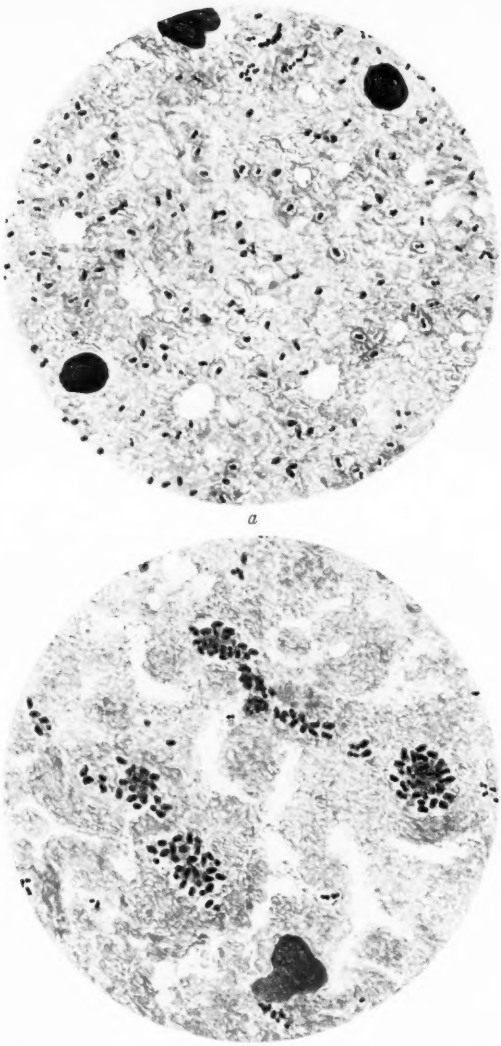

Fig. 126.—*a*, Stained smear of peritoneal exudate in the mouse, obtained in response to the injection of sputum mixed with heterologus serum (patient suffered from Type II pneumococcus pneumonia). *b*, Same, mixed with Type II serum, showing agglutinated organisms with smaller, darker staining capsules.

14 types.[1] The records of the Harlem Hospital Station of the Littauer Pneumonia Fund of New York University show that from September 17, 1928 to March 13, 1929, 374 cases of pneumonia were observed. Their distribution was as follows:

Type.	Number of cases.	Percentage of total cases.
I	91	24
II	33	9
III	30	3
IV	9	2½
V	28	8
VI	2	
VII	19	5
VIII	13	3
IX	12	3
X		
XI	1	
XII	3	1
XIII	4	1
XIV	4	1
x Group	119	31

In the Type I cases the percentage mortality was 14 per cent. in those treated with serum. The mortality in the non-serum Type I cases was 32 per cent. The mortality for the other types varied from 14 to 50 per cent. For some of these types there have been prepared specific therapeutic serums.

This rapid microscopic detection method has an important corollary. It occurred to us that if we could determine the type of organism by adding diluted serum to it, we might determine the presence of agglutinins in the patient's serum by adding to his serum specific antigen or organisms of the type invading the patient. Such a preparation is stained and examined for agglutinated pneumococci. If polyvalent serum has been used the organisms of the second type are added to another drop of serum on the same slide. This is now the basis of our dosage and for the frequency of the administration of serum in patients suffering from pneumonia.

[1] Four additional types have been segregated from group *x* up to June 1, 1929.

In effect, we are using a stained slide "Widal" applied to pneumonia patients to determine the presence of either natural or passively transferred immunity, measured by agglutination. It is to show the application of this method that the present clinic is held. The method is as follows: a capillary tube 3 inches in length, such as is used in dispensing smallpox vaccine, is touched to a drop of blood at the finger tip or ear. The blood enters the capillary and is allowed to clot. In order that no undue heat shall be applied to the tube, the tube is sealed by dipping one end into melted paraffin; the tube is then centrifuged. One of the empty capillary tubes is now drawn out in the flame to such a caliber that it can be inserted into the capillary in which the blood has been collected, the serum is then drawn up and may be expelled on a slide and mixed with organisms in the broth culture of the blood taken from the patient or the mouse's heart or with a formalinized suspension of organisms of appropriate type.[1]

PNEUMOCOCCUS PNEUMONIA TYPE VII. SPONTANEOUS DEVELOPMENT OF ANTIBODY AS TESTED BY AGGLUTININS

Case I.—The first patient this morning is Daniel McN., a very interesting case. This patient had pneumonia due to pneumococcus Type VII, with a negative blood-culture. He came in the serum series and pending the result of the typing received three doses of Types I and II serum with no apparent effect upon the temperature. The serum was discontinued and on the ninth day his temperature fell to normal. On the tenth day and subsequently he showed agglutinins for Type VII. There were no agglutinins for Type I, although serum of that type and Type II had been given. No test was made for agglutinins of Type II as they would run parallel with Type I. This patient developed his own immunity for Type VII as revealed by this test. The Types I and II serum antibody were excreted and yielded accordingly no permanent protection.

[1] I have since simplified this technic, mixing the antigen with a drop of blood directly upon a slide at the bedside. The blood may also be collected in a capillary tube and the serum expressed upon a slide and mixed with antigen without centrifugation.

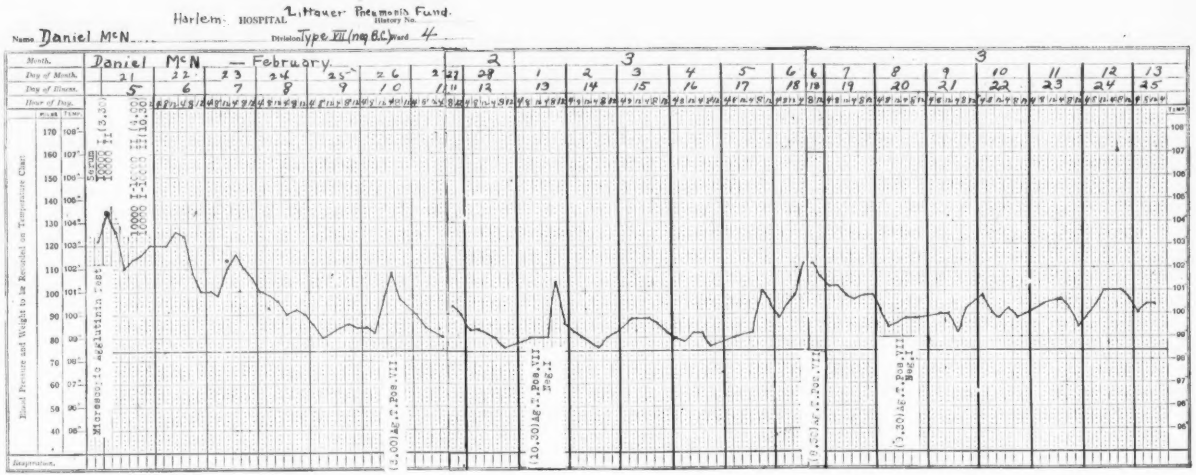

Fig. 127.—Case I. The notations indicate days when autogenous agglutinins for Type VII were revealed in the test (patient suffered from Type VII pneumococcus pneumonia).

Case II.—Joseph E. was also treated in conformity with the method described above. He was admitted, suffering from pneumonia due to pneumococcus Type I, on the second day of his illness and received serum in large doses. His temperature fell to 101° F. on the third day, but on the fourth day it rose. He was given a very large dose of serum, after which his temperature fell to normal. The agglutinin test on that day and on the following morning showed agglutination for Types I and II. This positive agglutination continued throughout the seventh day. His temperature rose on the evening of the seventh day and on the morning of the eighth day agglutinin was still present, though his temperature was high. In the afternoon and evening no agglutinins could be detected and another dose of serum was given. The agglutinins were present the next morning. During this ninth day another dose was given because the temperature was still high. On the morning of the tenth day the agglutinins were present for Type I and not for Type II. Apparently they were present, though not detected, because the next day they were detected in both Types I and II. From this time, as long as the patient was under observation, agglutinins were detectable for Type I, but not for Type II.

It is probable that the agglutinins detected on the eleventh day and afterward were those formed by the patient in response to the pneumonia. The absence of detectable agglutinins for Type II when equal amounts of Types I and II serum had been administered indicated this, for there is no reason to believe that the agglutinins of the different types disappear at unequal rates, and it has been found that the agglutinins are either entirely excreted in forty-eight hours or what remain cannot be detected by this method.

Fig. 128.—Case II. Shows the continued presence of agglutinins for Type I pneumococcus after serum had been injected in sufficient dose. Later, autogenous agglutinins for Type I appeared.

Fig. 128.—Case II. Shows the continued presence of agglutinins for Type I pneumococcus after serum had been injected in sufficient dose. Later, autogenous agglutinins for Type I appeared.

TYPE V PNEUMOCOCCUS WITH STREPTOCOCCUS IN PELVIC EXUDATE

Case III.—Delphine R. shows the help that an agglutination test gives in deciding whether an organism recovered from the sputum has actually invaded and produced disease in a patient. This patient was admitted on February 27, 1929, to the service of Dr. di Palma, the gynecologist, with pain in her abdomen of thirteen days' duration, chills and fever, dyspnea; the pain was in the right lower quadrant. Her present illness began on February 15th. She had missed her February menstruation. When the period was overdue five days, at a friend's suggestion she introduced into her cervix uteri a twig obtained from some Spanish plant. She accomplished this by the guidance of her own finger and an hour later commenced to pass blood. The following day she was taken ill with chills, fever, and pain over the lower abdomen. After the first chill the bleeding stopped for three days and then began again more profusely than before. She vomited once.

She has two children. She had an abortion at four months six years ago. Physical examination on admission: lungs were resonant throughout. Under ether about 6 ounces of serosanguineous pus were drained and a tube was inserted in a colpotomy incision. The blood count was 13,000 with 94 per cent. polynuclears. Her temperature rose the following day to 103.8° F. and her pulse to 144. A consultation with the Pneumonia Service was requested, and that evening I found the following:

A marked ileus with definite rigidity of the abdomen. The diaphragm was displaced upward. The heart sounds were obscured. There was bronchial breathing over both lower lobes, and a friction rub on the right side. Respirations were 40. In view of the fact that there was a pelvic infection, it seemed probable that this patient was suffering from a general streptococcus sepsis with involvement of the right lung. A blood-culture was taken and, as she was a serum case by reason of her order of admission to the Pneumonia Service, serum for Types I and II was administered. A postanesthetic pneumonia could not be excluded. Because of the possibility that streptococci might be invading

her lung, the possibility that they might be of a scarlatinal strain was considered. Accordingly 25 c.c. of scarlet fever serum was administered intramuscularly. This was repeated the following morning. She was placed in an oxygen tent. Her condition improved. No organisms grew in the blood-culture. Some white mucoid sputum was injected into a mouse and revealed a Type V pneumococcus. A culture from the heart's blood of the mouse showed an organism of Type V also the following morning. On the fifth day her temperature had fallen to 100° F., her pulse was 98, and she was able to leave the tent.

We were now confronted with the interpretation of our observations. Was this patient a carrier of Type V organisms or was this pneumococcus the actual invader of the lung? Was this a lobar pneumonia in a patient infected with a streptococcus pelvic cellulitis or had we a streptococcus pulmonary invasion?

Subsequently, when the patient was able to be moved, we discovered by radiography that there was a diffuse homogeneous clouding of the right pulmonary field. This was not decisive, as the shadow would be the same regardless of bacterial invader. Our doubts were clarified, however, by a study of the patient's serum agglutination. On the twelfth day after the serum had been injected we found that the patient had agglutinins for Type V and none for Type I. This observation was repeated on the fifteenth day. On the twenty-sixth day these agglutinins had disappeared. Although the patient had continued to run a septic temperature for three weeks, her general condition was well maintained. The positive agglutination test which appeared and lasted at least two weeks may be taken as evidence that the pneumonia was actually due to a Type V organism and not to a streptococcus invasion. Had no agglutinins appeared we should have been compelled to believe that she was merely a carrier of Type V pneumococcus.

In this connection let me narrate the history of another patient, Case IV, where the failure of agglutinins to appear and the absence of developed immunity led us to contend that the patient merely carried one organism found in the sputum which had not become pathogenic.

A CASE IN WHICH ONE PNEUMOCOCCUS IS RECOVERED FROM THE PERITONEUM OF THE MOUSE AND A DIFFERENT ONE FROM THE MOUSE'S HEART ON TWO OCCASIONS

Case IV.—Mr. L. came into the hospital for the second time on March 16, 1929. On his first admission in December, 1928, he was quite ill. We recovered a pneumococcus Type VII from the peritoneal exudate and an organism of the *x* type from the blood of the mouse's heart. He was delirious and had an otitis media complicating his illness. After he was discharged he was apparently well until March 16, 1929, when he had a pneumonia of the opposite lower lobe. Before his record had been looked up we had a report of Type VII pneumococcus from the peritoneal exudate of the mouse that had been injected with his sputum. The next day the blood of the mouse's heart was again *x* type. During our observation of this man he has never developed any demonstrable agglutination against Type VII pneumococcus.

Neither have we been able to demonstrate agglutinins against the other invading organism. We cannot tell whether the organism which we removed, but did not identify, is the identical organism with which he was previously invaded, as we did not keep his first culture.

In view of the absence of Type VII agglutination it is probable, though by no means conclusively proved, that this Type VII organism which did not invade the mouse's blood-stream is not pathogenic and that the patient is merely a carrier of Type VII.

Recognition of the specificity of the organisms formerly grouped as Group IV will prove of great importance in connection with the epidemiology of pneumonia.

Dr. Schroeder of the Research Laboratory of the New York Department of Health recognized an epidemic due to one of these organisms in an orphan asylum where there had been an epidemic of respiratory infection with some pneumonias. Twenty per cent. of the children in only one pavilion were affected. Until the specificity of the invader was recognized bacterial studies were futile in determining the excitant. A Type V pneumococcus was found in 7 of 9 cases studied.

ADMINISTRATION OF SERUM GUIDED BY AGGLUTININ DETECTION

Case V.—Mr. H., the next patient, who had had a pneumococcus Type I pneumonia, illustrates the safety of withholding serum treatment in the presence of elevated temperature when agglutinins for the invading type have developed. This patient's temperature finally fell to normal two days after the last

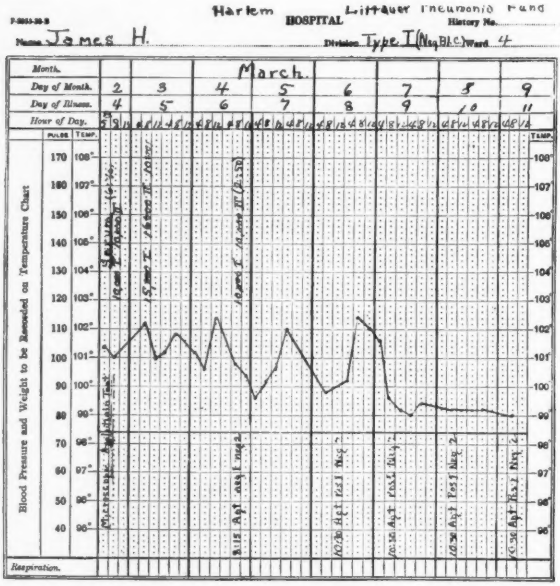

Fig. 129.—Development of autogenous agglutinins for Type I detected thirty-six hours after last dose of serum. Though temperature rose again, serum was withheld.

dose of serum given on the sixth day. On the eighth day of his illness his temperature was still elevated to a point where serum should ordinarily have been administered. Although he had agglutinins for Type I, they were negative in the control for Type II which had been administered thirty-six hours previously. In spite of the rise of temperature to 102.4° F., which is usually an indication for the administration of serum, no serum was

given. His serum continued to show the agglutinins and he made an uneventful recovery. The agglutinins which were subsequently demonstrated were doubtless produced by his own mechanism for the purpose in response to his disease.

BACTERIEMIA, PNEUMOCOCCUS TYPE I, CONTROLLED BY ANTIBODY. DOSAGE GAUGED BY AGGLUTININ STUDY—DISAPPEARANCE OF AGGLUTININS IN PRESENCE OF EMPYEMA

Case VI.—T. A. was admitted on the fourth day of his illness, which had commenced with severe pain in the right chest aggravated by cough on inspiration. From the outset he had had bloody sputum and severe frontal headache. For the first three days he vomited continuously. He complained of dyspnea. The signs on admission were those of consolidation involving the entire right side, with pleurisy. He was rated at 30: involvement 10, respiratory rate 5, headache 5, pulse-rate 10, cyanosis 10, distention 5, and bacteriemia 20. He was icteric.

On admission the routine test revealed that there was no antibody for Types I or II. The sputum revealed Type I in the mouse's peritoneal exudate and in its heart's blood-culture. The blood-culture from the patient showed 290 colonies Type I pneumococcus in one plate and 310 in the other.

After the first dose of serum, and when it became known that his blood-culture was positive, he was given polyvalent serum containing 60,000 units of Type I, and his antibody was again taken. It was negative for Types I and II. That evening he received 20,000 units additional. The blood-culture taken on the second day after admission, the sixth day of his illness, was still positive in the broth; however, there was no growth on the plates. The blood-culture taken on the next day was negative.

As the chart (Fig. 130) indicates, he was given polyvalent serum containing 10,000 units Type I and 10,000 units Type II per cubic centimeter in doses sufficient to reveal a positive antibody. On the fourteenth day of his illness, in spite of the large dose of serum on the thirteenth, his agglutination was negative in Types I and II. After the last two doses of serum, which were of the identical lot as those previously administered, he had a

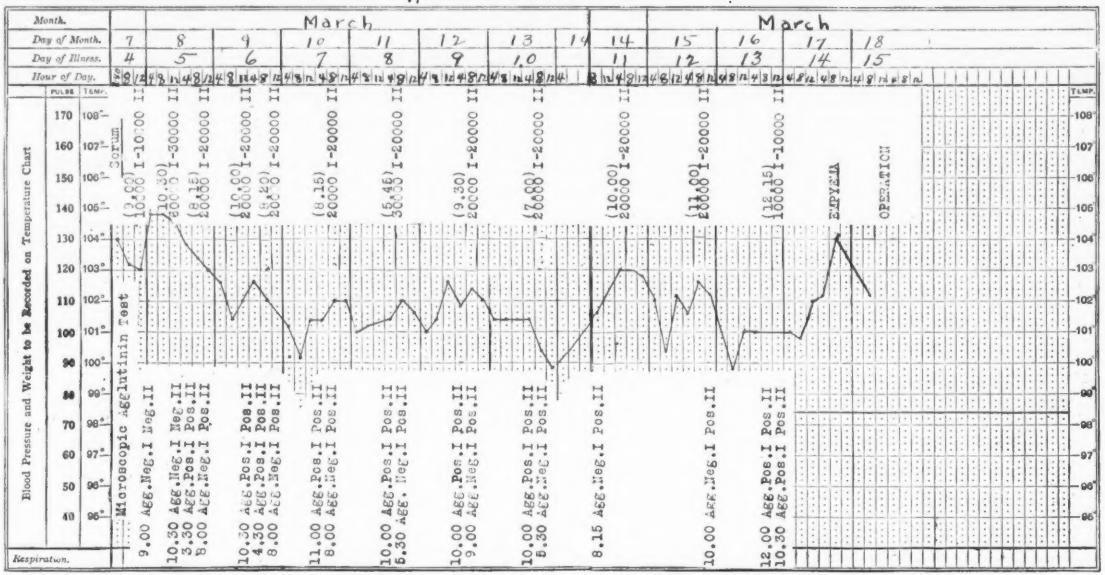

Fig. 130.—Type I pneumococcus pneumonia admitted on seventh day of illness with marked bacteriemia. Treated with serum; dosage controlled by agglutinin study. Agglutinins absorbed by pleural exudate, so that agglutination test became negative later. Disappearance of a large amount of agglutinin in the absence of bacteriemia suggests collection of pus.

severe febrile reaction and his temperature rose to 104° F. At this time the signs of fluid in the right chest seemed definite. He was aspirated and pus was obtained. He was operated that afternoon. Since operation his convalescence has been uneventful.

Comment.—This case shows the importance of large doses of serum early in the disease when the blood-culture is positive. It also points out the fact that late in the disease where there is a failure in spite of large doses to maintain a detectable agglutinin concentration in the blood-stream, an accumulation of pus which absorbs the antibody as fast as it is injected must be suspected.

THE WITHHOLDING OF SERUM IN A PATIENT WHO WAS DEVELOPING HIS OWN ANTIBODY—CRISIS PREDICTED

Case VII.—W. J. came in on the sixth day of his illness (pneumonia due to Type I pneumococcus) and received serum. He was so ill that he was placed in the atmosphere control room under an increased partial pressure of oxygen of 40 volumes per cent. He was delirious and was restrained. On the evening of the ninth day, when it was time to administer a dose of serum, we decided to determine whether antibody was present, although there apparently was no change in his condition and although his temperature was high. His blood-serum was tested at 6 P. M. and again at 11 P. M. On both occasions agglutinins were evidenced for Type I and apparently to a greater degree with the second test. Serum was withheld. That night he had his crisis and after that agglutinins continued to be present for Type I.

It is quite evident that he was producing his own agglutinins and that we were correct in forecasting the crisis and withholding serum as unnecessary.

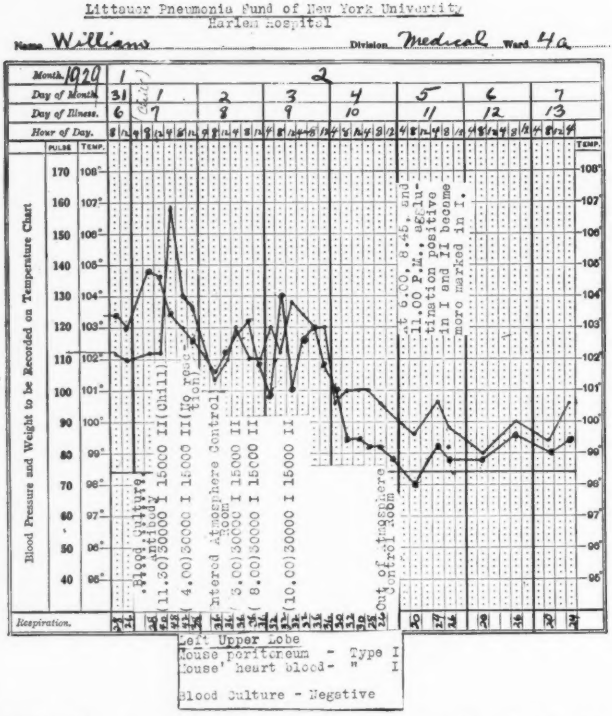

Fig. 131.—Serum case, Type I pneumococcus pneumonia. Serum withheld when specific agglutinins were detected. Crisis predicted.

INADEQUATE DOSAGE IN TYPE I BACTERIEMIA UNCONTROLLED BY AGGLUTINATION TESTS

Case VIII.—E. J. was a patient with a positive blood-culture in whom tremendous doses of serum were employed and yet the patient died. This case was seen before the development of Sabin's technic. The serum administration had not been checked by our microscopic slide agglutination method from the onset.

VALUE OF ADMINISTERING ANTIBODY FOR PNEUMOCOCCUS TYPE I BEFORE THE TYPE HAS BEEN DETERMINED. A CASE WHERE SPUTUM EXAMINATION WAS MISLEADING. EXCITING ORGANISM RECOVERED FROM EMPYEMA PUS

Case IX.—Mr. C. In spite of our insistence upon early typing, the case we are now presenting represents the difficulties sometimes encountered and supports our contention that it is wise practice to give all patients suffering from pneumonia doses of polyvalent serum of Types I and II, pending the more accurate determination of type.

Mr. C. was admitted on the fifth day of his illness. He had suffered for some time with a cough. For the past five days he spat blood. During the past three days he complained of persistent hiccough. He has been subject to hiccough on many occasions in the past and has suffered from gastro-intestinal upsets.

On admission he was an acutely ill man with marked supraclavicular dulness over the right upper lobe and many crepitant râles. There was bronchial breathing and bronchophony. On the left side there was impaired resonance and bronchovesicular breathing; anteriorly there was distant bronchovesicular breathing. Scattered squeaking râles were heard throughout the chest. There was a rough inspiratory and expiratory friction sound over the right lower lobe anteriorly. The apex of the heart was diffuse in the fifth space about 9.5 cm. to the left of the midline. A diagnosis of acute pulmonary phthisis was made with a right abdominal diaphragmatic pleurisy.

On the day after admission the patient appeared to be more acutely ill. He was markedly dyspneic, with movement of the alæ nasi in respiration. There was marked dulness and bronchial breathing with egophony over the right upper lobe and more numerous crepitant râles. There was dulness to a less degree over the remainder of the right lung with fine moist crepitant râles. He was still hiccoughing and there was marked distention. That afternoon the diagnosis of pneumonia was confirmed by the visiting physician and the patient was referred to the Pneumonia Service.

There was marked distention throughout the abdomen, more marked in the center of the abdomen, later there was marked distention of the left upper quadrant (gastric). The hiccough involved both sides of the diaphragm, occasionally the right alone and occasionally the left. At times it was followed by a spastic contraction. That night his condition was poor. His respirations were 38. He was delirious and apparently toxic. His distention was treated with enemata of asafetida and with turpentine stupes. His hiccough was controlled by the administration of carboxygen, which is 5 per cent. CO_2 and 95 per cent. oxygen. The rationale of this treatment is that the CO_2 causes such a marked stimulation of the respiratory center that the normal rhythm of the diaphragm may be restored. This procedure involves no oxygen deprivation which might embarrass the heart. The carboxygen had to be reapplied several times, as often sometimes as once an hour and again at several hour intervals, but invariably after five or ten minutes' application the hiccoughs ceased.

The patient was rated at 55. The entire right side of the lung was involved. The rating: involvement 10, respiratory rate 5, deliriousness 10, rapid pulse 10, cyanosis 5, and distention 10. The patient had to be catheterized on a number of occasions. The sputum was green and mucoid and contained a few Gram-positive diplococci which were bile soluble. The mouse was sick at the end of twelve hours and its peritoneal exudate did not cause precipitation in any of the tubes. On two occasions no growth in cultures of the blood from the mouse's heart occurred. Finally on the fourth day of observation a miscellaneous group organism was obtained from the peritoneum and also from the heart's blood of the third mouse. The patient's blood-cultures were negative. On the seventh day of his illness the patient's pulse was 160, although his temperature was only 101° F. On the ninth day his temperature rose to 102.3° F., the pulse was 120, and he was placed in the atmosphere control room under an increased partial pressure of oxygen, 40 volumes per cent. His hiccoughs returned from time to time in the chamber, and carboxygen was applied as before.

Several sputum examinations failed to show tubercle bacilli. The patient continued to hiccough from time to time until the twenty-second day of his illness.

After entering the chamber his temperature and pulse fell to normal and continued normal for three days. Then the temperature again reached 103° F. and his pulse 114. The signs were apparently unchanged. On the fifteenth day his temperature fell to 100° F. and his pulse to 96. He was taken from the chamber and his temperature immediately rose to 103° F., pulse 120. The temperature continued for a day, fell to normal, then rose again, and fluctuated around 101° F. On the twenty-fifth day his chest was tapped, but only sufficient pus could be obtained for a smear and culture. This pus revealed a Type I pneumococcus. The temperature continued to fluctuate around 101° F., but the patient's condition improved. Finally, on the thirty-sixth day of his illness, the temperature was 100° F. and the pulse 104. The signs of fluid were now unequivocal. Aspiration produced thick pus and, accordingly, the following day he was drained with a rib resection. Since then he has convalesced satisfactorily.

PNEUMOCOCCUS TYPE I INVASION OF PATIENT WITH PULMONARY TUBERCULOSIS. ORGANISMS OF CORRECT TYPE DISCOVERED BY MICROSCOPIC STAINED SLIDE TEST SHORTLY AFTER INOCULATION, THOUGH THERE WERE INSUFFICIENT ORGANISMS FOR TYPING NEXT DAY. EARLY TREATMENT APPARENTLY PREVENTED DEVELOPMENT OF AGGLUTININS

Case X.—J. P., the last patient this morning, is a man fifty-two years of age. He is the morgue keeper at our hospital. He had a cold for a number of days before coming under our observation on the ward. He has had a number of colds this winter and we have all known for a long time that he has had tubercle bacilli in his sputum, although his temperature, pulse, and respiration have been normal. He is an alcoholic, drinking to excess either constantly or periodically. An epididymitis was operated on thirty years ago.

At 11 P. M., March 11th, he had a chill lasting fifteen minutes. This was followed by fever, profuse sweating, and cough pro-

ductive of colorless or yellowish-green mucus. On March 12th he awoke with a chill that lasted ten minutes and was followed by fever, sweating, and a sharp pain in the left chest aggravated by cough and on deep inspiration. He had a slight cough and a dull headache. On admission to the ward his temperature was 104.6° F., his pulse 102, and his respirations 36. He is a thin, undernourished white adult who appeared to be acutely ill, complaining of feeling chilly, and of severe pain in the left chest with a persistent irritating cough. There is a corneal opacity in the left eye. There was slight dulness at the angle of the left scapula. No friction rub was noted, but at the angle of the scapula the breathing was definitely higher pitched and bronchovesicular in character. There was dulness over both apices and a few fine crepitant râles. The heart was not enlarged, the sounds were of fair quality. There was no murmur.

On admission the patient was rated at 45 in accordance with our rating system: 5 for involvement, 10 for rate, 5 for pleurisy, 5 for headache, 5 for cardiac rate, and 5 for cyanosis. He was penalized 10 for alcoholism, 5 for his age, and 5 for tuberculosis. A pleuritic friction was definitely heard during the morning. The sputum was injected into a mouse. Four hours later some of the peritoneal exudate was drawn by capillary action. It showed Gram-negative diplococci which agglutinated with Type I serum. The next morning the mouse was killed, but there were insufficient organisms for the regular typing. There was no agglutination with any of the serums. A culture of the blood of the mouse's heart revealed Type I organisms on the following day.

After the blood-culture was taken a routine agglutination test was performed for Types I and II serum. This proved negative. He was given 10,000 units of Types I and II serum at 2 P. M. That night an agglutination test was performed. There were no agglutinins for Type I, but there was agglutinin for Type II. The serum was repeated at midnight, 20,000 units of Types I and II. The temperature was 105° F. before the serum was administered, but fell during the night to 98.8° F. The pulse fell to 96. During the remainder of the day agglutinins were

demonstrable in both Types I and II. The following morning the agglutinins were not demonstrated and another dose of serum was given, 10,000 units Type I and 10,000 units Type II. There was no febrile reaction after any doses of the serum. A week later there were no agglutinins for Types I or II. Apparently this patient did not produce his own antibody demonstrable

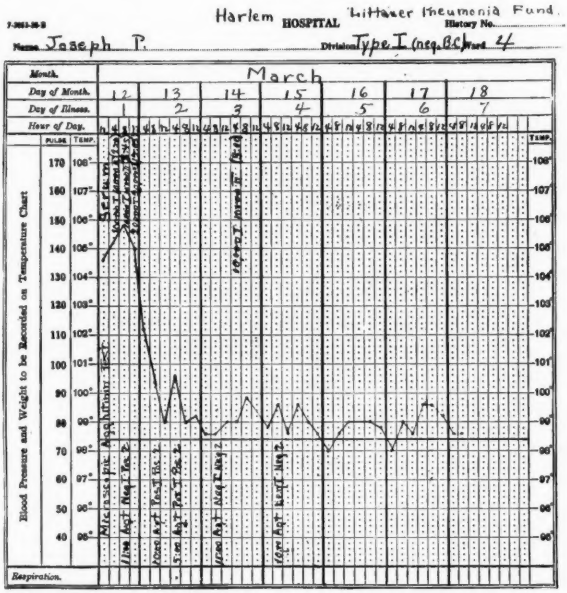

Fig. 132.—Type I pneumococcus pneumonia with prompt termination of illness by specific antibody administration, controlled by agglutinin tests. Failure to develop autogenous agglutinins.

as agglutinins in sufficient concentration to be demonstrated by our tests.

One might explain this condition by assuming that either there were insufficient organisms or that the organisms were not permitted to stimulate the agglutinin production mechanism for a sufficient length of time. This may have been due to the early and effective administration of the antibody.

This patient developed a slight rise of temperature which reached 102.4° F. on the eighth and tenth days of his illness, with pains in his joints and erythematous eruption over the anterior surface of the left forearm and arm, and also a macular papular areolar surface of the left forearm and arm, as well as a macular papular areola about the point where the needle had been inserted into the vein. During this serum reaction there was also a marked conjunctivitis. It is possible that the chronic tuberculosis was responsible for this altered reaction. The patient has since made an uneventful convalescence.

This patient shows not only the importance of the new method of typing, but he also exhibits several interesting points in connection with the more modern serum treatment of pneumonia: first, the importance of the new Sabin microscopic agglutination test and my modification; second, the importance of observing the presence of agglutinin in connection with the serum therapy, and, finally, the effectiveness of early treatment in preventing the occurrence of autogenous agglutinins by curtailing the invasion.

SUMMARY

The most important lesson learned from the observation of these patients is the value of gauging the amount of antibody required in the treatment of those suffering from pneumonia.

Antibodies must be produced if patients are to recover from pneumonia. One of these antibodies is the agglutinin, which, by the method described, is readily detectable. Apparently agglutinin does not run parallel with the protective antibody. Dr. Park has found that agglutination is usually proportionately greater in horses shortly after antigen inoculation is commenced, and agglutinin diminishes while the protective antibody is still quite high. The slide agglutination test is three times more sensitive than the macroscopic agglutination technic described by Arlyle Noble and adapted by Baldwin to pneumonia studies.

There is no method of detecting protective antibody in less than forty-eight hours unless it shall be found that opsonins run parallel with protection. Agglutinin may be detected in a

few minutes, and it has accordingly been employed as a dose gauge. In this way an excess of protective antibody may be administered, but that is less serious than an insufficient supply.

The temperature (rectal temperature of 102° F. or above) has been used as an indication for antibody administration in most of our studies. Had we used the agglutination test we might have stopped earlier in some cases, but in others we should have continued to give it for a longer time. It is possible that the total amount of serum consumed would not have been greatly changed, but lives might have been saved had we employed this guide consistently and earlier because an excess of antibody apparently can do no harm.

CLINIC OF DR. HAROLD E. B. PARDEE

NEW YORK HOSPITAL

THE IMPORTANCE OF THE ETIOLOGY IN THE DIAGNOSIS OF HEART DISEASE

IN the diagnosis and treatment of patients with heart disease attention used to be centered upon the pathologic condition. The facts of the history and examination were used as a basis for deducing the variety and extent of the pathologic changes within the patient's heart, and only too often consideration was given to little else than this pathologic diagnosis. This led easily to errors in treatment and prognosis, so that in time the fallacy of this sort of diagnosis was recognized and the view broadened. The cardiac diagnosis as understood at present must include not only the pathologic condition but also an understanding of the cardiac mechanism and of the functional capacity, and also of the etiology of the disease. The importance of understanding the etiology of our patient's disease is often overlooked, and it is in order to bring this phase of cardiac diagnosis to your attention that we are going to discuss today three patients, each of whom shows a similar pathologic condition. These three patients all have aortic insufficiency, and it will be shown how their clinical condition and their treatment depend upon the fact that the etiology in each case is different.

Case I.—Mr. H. C., twenty-six years of age, complaining of weakness and palpitation for a week, so that he finally had to give up his attempts to go to business. The palpitation was felt on exertion, but there were also times when he was sitting about or lying in bed when it would come spontaneously. It would on these occasions feel something like heavy thumps of the

heart coming irregularly. Five years ago he had had an attack of acute rheumatic fever with a temperature running for several days in the neighborhood of 100° F., and with involvement of several joints. At this time a heart murmur was found. His activities were carefully restricted during convalescence, but for a time he found that walking for more than four or five blocks at an ordinary rate would cause palpitation. This passed off after several months, and in the interval he has considered himself perfectly well. He has had no further pain in the joints or in the muscles and has had no sore throat. Five and one-half years ago he had an attack of grippe, and ten years ago an attack of pneumonia. At the time of the grippe attack the attending physician observed that he had some trouble with his heart. During childhood he had measles and whooping-cough, but no scarlet fever; sore throats were not especially noticed and venereal infection was denied.

The present examination discovered that he had a temperature of 100° F. by mouth, the pulse was 90, regular, full, and of the collapsing type. The blood-pressure was 145 mm. systolic and 40 mm. diastolic. The heart was moderately enlarged, the cardiac dulness extending 12 cm. to the left of the midline in the fifth space, which was 2 cm. beyond the midclavicular line. Dulness extended 2.5 cm. to the right. In the second interspace the width of the dulness was 8 cm. The apex beat was heaving and its maximum was just inside the left border of dulness. The first heart sound at the apex was obscured by a definite, blowing systolic murmur. There was also heard a rumbling diastolic murmur at the apex, without any presystolic accentuation. At the base and over the body of the heart, with its maximum at the left border of the sternum in the fourth space, there was a definite, long, blowing diastolic murmur; and over the aortic area, a faint, rather rough, short systolic murmur. The neck showed rather forcibly pulsating carotids, but there was no abnormal venous pulsation. The thyroid was normal; the cervical lymph-nodes were not enlarged; the tonsils were small, slightly reddened, but did not seem to contain much detritus. The abdomen was normal in appearance, the liver was not made

out to be enlarged; the spleen, however, was just palpable below the ribs. There was no edema of the extremities. The vital capacity was normal for one of his height.

The orthodiagraphic tracing of his heart is seen in Fig. 133. It shows an enlargement of the ventricular area, the transverse diameter of the heart being 13.5 cm., which is well over one-half of the total chest diameter, which is 23 cm. The ventricles lie rather transversely. The outline of the aorta is somewhat dilated and shows very marked systolic and diastolic excursion, as do also all parts of the heart.

Fig. 133.—Orthodiagraphic tracing of the first patient. "R" and "L" refer, respectively, to the inner portion of the right and left thoracic wall.

The electrocardiogram is seen in Fig. 134. It shows normal auricular waves (P). The auriculoventricular conduction time is normal, P-R measuring 0.16 seconds. The QRS group shows neither right nor left axis deviation, so that one would say that neither ventricle is predominantly hypertrophied. The T wave is turned downward in Lead II, and as the patient has not taken any drug which might have caused this, we believe that it indicates the presence of myocardial disease.

This young man, then, is suffering from a disease of the aortic valve with insufficiency. There is also an insufficiency of the mitral valve. There is cardiac enlargement and dilatation

of the aorta. Likewise myocardial disease is present as shown by the abnormality of the electrocardiogram. Considering the heart from the point of view of its mechanism, we find that the rhythm is normal. The systolic murmur which is heard at the apex indicates an insufficiency of the mitral valve, which might be due either to a disease of this valve or to a functional incom-

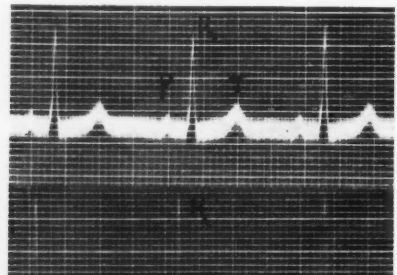

Fig. 134.—Electrocardiogram of first patient, showing the inverted T wave in Lead 2 which indicates the myocardial disease.

petency. This is a matter of speculation rather than of diagnosis, but in view of his condition it is very possible that this mitral insufficiency is not due to disease of the mitral valve, but to a leakage of this valve resulting from weakness of the papillary muscles or of the ring which supports the mitral valve. The functional capacity of the heart is but little impaired. He is

able to walk freely and even to climb stairs without becoming short of breath, and feels palpitation only on efforts which are rather above the average in their severity. He falls into the functional class 2A, as adopted by the American Heart Association.[1]

We have diagnosed the structural abnormalities and the functional defects of this heart, but until we have realized that the etiology of the disease is rheumatic we have not properly understood the condition of our patient. It is not difficult in this case to say that the disease is rheumatic because of the plain history of a rheumatic attack five years ago, but the importance of this fact is tremendous. Reviewing his history we find that heart disease was discovered before his rheumatic fever five years ago, and that following this attack he had some few symptoms referable to the heart, which suggests that at that time the cardiac condition was added to. His condition at present, with slight temperature and symptoms referable to the heart, without much evidence of cardiac insufficiency indicates that the rheumatic infection is again active within the heart. So we are dealing not only with a chronic rheumatic valvular disease but also with an acute exacerbation of rheumatic cardiac infection. It is interesting and remarkable how in some patients the rheumatic infection remains dormant for months or even, as in this case, for years, and will then recur. It is also remarkable how minor a part the joint manifestations may play in some rheumatic cases. This patient apparently had a cardiac lesion before the first appearance of joint involvement, and this present exacerbation is wholly unaccompanied by an inflammation of the joints.

He shows one feature which, on the whole, is uncommon in patients with rheumatic heart disease, although it is more common in the acute stage than in the chronic. The abnormality of his electrocardiogram, the downward T wave probably indicates that there is an acute inflammatory reaction in the

[1] See Criteria for the Classification and Diagnosis of Heart Disease, J. H. Bainton, R. L. Levy, W. C. Munley, and H. E. B. Pardee, Hoeber, New York, 1928.

myocardium at present. The T wave changes of acute rheumatic involvement usually pass off as the inflammation subsides, and after the attack, when healing has taken place, his electrocardiogram may again be quite normal. Occasionally, however, the electrocardiographic changes may persist, and in these cases we feel that the myocardial lesion has also persisted in some form, possibly a chronic inflammatory process and probably a fibrotic one.

Another interesting feature about this patient is the excellent functional capacity of the heart during the last five years, when he must have had a very definite valvular lesion. Even at present, with a myocardial involvement, the functional capacity is but slightly impaired. This is one of the many instances which has served to show us that a prognosis as to ability to exercise cannot depend upon the anatomic lesion.

As to the treatment of this patient, he should be at rest in bed, not because of any evidence of cardiac failure, but because we know that he has an acute inflammatory reaction in his myocardium, and that, therefore, his myocardium should not be subjected to any more work than is absolutely necessary. His diet is not so important; it should be a general diet composed of easily digestible, simply cooked food of all classes. His fever is so slight that I do not believe that any sort of food need be proscribed. He should drink plenty of water during the day and should be given sodium salicylate in spite of the fact that there are no evidences of rheumatic joint involvement. The salicylates have an evident effect on the disease process in the acute rheumatic joints, and it seems very likely that it has a similar effect upon all acute rheumatic inflammation. As long then as he continues to have fever or leukocytosis he should be given salicylate therapy, starting perhaps with 30 grains of sodium salicylate and sodium bicarbonate, four times daily, given well diluted in milk; this should be continued until the fever has been normal for four or five days, when the dose may be reduced to 20 grains, and this continued until the fever has been normal for ten days, and the leukocyte count is normal. It has been found that leukocytosis is an important sign in the patient with

acute rheumatic manifestations because it will often be present when the fever is normal. Patients whose treatment has been stopped when they still have a leukocytosis seem especially prone to have a prompt relapse or recurrence of the fever.

This patient shows very little evidence of cardiac insufficiency, and, accordingly, the administration of digitalis is not indicated. It is only patients who come in class 2B and 3 who need to take digitalis.

The prognosis in such a case is dependent upon the severity of the anatomic lesion, the tendency for acute rheumatic exacerbations to recur, and the patient's ability to avoid physical strain and exposure to cold and damp. The rôle of the tonsil in prognosis is not yet decided. Many claim that the removal of tonsils tends to diminish the frequency of rheumatic recurrences. This is not wholly proved at present, but it is my personal feeling that tonsillectomy is a minor operation, and is not at all likely to harm the patient, whereas the possibilities of a serious invasion of the heart following a tonsillitis or a peritonsillar abscess cannot be denied. It is my feeling, therefore, that all patients with rheumatic valvular disease should have the tonsils removed, irrespective of whether these tonsils appear at the time to be infected or not. There is no examination of the tonsils which will positively tell us whether they may or may not in the future become a source of bacterial invasion of the system.

This patient, then, should have the tonsils removed, and as he is engaged in a sedentary indoor occupation, he will be protected from physical overstrain and from exposure to deleterious climate. The extent of his pathologic lesion before this attack was not so great as to seriously handicap his heart function and it is possible that after this attack the situation may be much the same, so it would seem as though he could look forward to many years of freedom from cardiac symptoms, provided that he does not have future rheumatic invasion.

Case II.—Mr. B., forty-six years of age, began to be troubled nine months ago by palpitation, especially if he walked fast or

if he became excited. If the effort or excitement continued, a pressure sensation was felt over the anterior chest, at the level of the second and third ribs near the midline, and he would lose his strength and feel weak, and break out with a perspiration. This sensation would force him to lie down and rest, and he usually recovered promptly. During the last three months he has found it necessary to rest after climbing a part of the subway stairs. During the last two months he has had rare attacks when he was at rest, when there was no element of effort or excitement to bring them on. These would last for five or ten minutes only. He does not notice shortness of breath, and has no real pain in his chest or elsewhere. No swelling of the legs has been noticed and he has no cough. He has had no previous illnesses since childhood when he had measles and whooping-cough; he has had only occasional sore throats, and venereal infection was denied.

There is nothing remarkable about his appearance, as you see. The pulse was 90 per minute and medium sized. The arterial walls were moderately thickened. The blood-pressure was 156/50. The radial and brachial arteries were moderately thickened. The apex beat was heaving, situated just outside the midclavicular line. The dulness extended 15 cm. to the left of the midline in the fifth interspace, which is 2 cm. beyond the midclavicular line. The dulness at the base extended 2.5 cm. to the left and 5 cm. to the right. The first heart sound at the apex was prolonged and faint, and there was a faint, long, blowing systolic murmur following it. The aortic second sound was ringing and markedly accentuated and was followed by a rough systolic murmur of moderate intensity. At the aortic area, and heard all over the heart, even at the apex, there was a long, blowing diastolic murmur of considerable intensity. The neck showed marked carotid pulsation, but no abnormal venous congestion or pulsation. The lymph-nodes of the neck were not enlarged. The tonsils appeared red, and it was found upon examination that there was a slight degree of edema of the ankles. The lungs were negative except for a few râles at the left base posteriorly.

The orthodiagraphic tracing appears in Fig. 135. It shows a definite enlargement of the ventricular area; the transverse diameter being 14 cm., whereas the transverse diameter of the chest is only 25.5 cm. The appearance of the aortic arch is striking. There is a marked dilatation, especially in the ascending portion, and it seems that the point of junction of the aorta and the right auricle is much lower down in this outline than it is in the rheumatic heart shown in Fig. 133. This is a marked aortic dilatation, and is especially localized in the ascending portion.

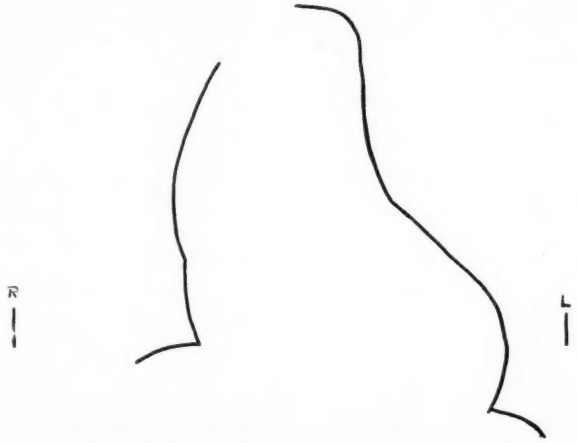

Fig. 135.—Orthodiagraphic tracing of second patient.

The electrocardiogram seen in Fig. 136 shows a normal rhythm, interrupted by occasional ventricular premature beats. These were infrequent and do not appear in the figure. The auricular waves are much wider than normal, the width on the base line measuring 0.12 second. The wave is also slightly above the usual normal figure in height, measuring 2.5 mm. The auriculoventricular conduction time is normal; P-R measuring 0.18 second. The QRS group showed a marked left axis deviation by the large S wave in Lead III, with the R much larger in Lead I than in Lead II. This relation of the waves is

not abolished by deep inspiration, and so we believe indicates an hypertrophy of the left ventricle. There is no abnormality of the QRS group or of the T wave to suggest the presence of myocardial disease.

This patient too has an aortic insufficiency with moderate cardiac enlargement. The aortic arch is dilated and almost aneurysmal. There is no evidence of disease of the myocardium.

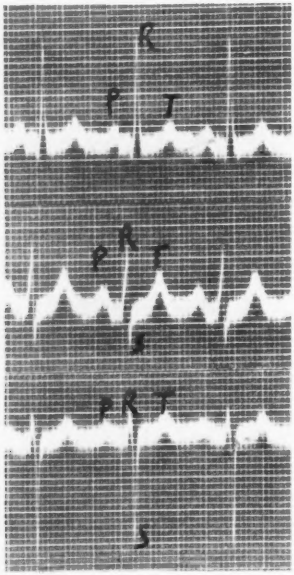

Fig. 136.—Electrocardiogram of second patient showing no significant abnormality except the left axis deviation of QRS.

The heart rhythm is normal usually, but at times there are ventricular premature beats. The functional capacity is of late more than moderately diminished, owing to the pressure sensation which appears in the chest. His functional classification would be 2B. Again there is some question about the diagnosis of the systolic murmur at the apex, whether it is due to disease of the mitral valve, or to an incompetency of this valve because of dilatation of the mitral ring. We shall return to this after a

discussion of the etiology, for the etiology has an important bearing upon this decision.

This man is rather late in life for an aortic insufficiency of rheumatic origin to first make itself known. The appearance of the aortic arch under the fluoroscope is very unusual for a patient with rheumatic valvular disease. It shows a marked dilatation—almost an aneurysm—such as might arise from a syphilitic aortitis. In spite of the negative history of venereal infection, and the patient was quite sincere in denying any knowledge of this, a Wassermann reaction was done and was returned 4+. This, of course, confirmed the idea that this patient's heart disease was due to syphilis, the diagnosis being suggested by the appearance of the aortic arch under the fluoroscope, and by the age at which the symptoms made their appearance.

Returning now to a consideration of the etiology of the murmur which was heard at the apex, it is more likely that this is due to an incompetency of the mitral valve than to a disease, for it is rare for syphilis to attack this valve. This is in marked contrast to the situation when the etiology is rheumatic, for then, as you know, the mitral valve is frequently involved.

The etiology of this patient's disease gives an important indication as to treatment, for if we did not diagnose the etiology we would not feel that he should be treated for syphilis; and this treatment is most clearly indicated by the character of the disease and the positive Wassermann. We must not only treat the symptoms which have arisen from the pathologic lesion in the heart, but we must treat the causative disease, for unless this is checked it will cause an extension of the pathologic changes.

The cardiac treatment in this case would consist of a mild sedative to diminish the patient's cardiac sensory mechanism, to quiet his general reflexes, and perhaps to check his tendency to hypertension. For this purpose we would give a mixture containing 3 grains of chloral hydrate and 10 grains of soda bromid to the dram of peppermint water, to be taken three or four times daily. Since it is felt that the palpitation is largely

due to the occurrence of the premature beats we should give quinidin sulphate in capsules of 4 grains, three times daily, to diminish the irritability of the heart and the frequency of the premature beats, adding to this some drug of the xanthin group, for its effect on the coronary arteries.

The myocardial effects of cardiovascular syphilis are almost entirely the result of narrowing of the coronary arteries, so that if a drug could be given to dilate these arteries and thus bring more blood to the muscle of the heart it should do good. The two most useful drugs for this purpose seem to be metaphyllin (euphyllin), which should be given in $1\frac{1}{2}$-grain doses three or four times daily, and theocalcin, which should be given in $7\frac{1}{2}$-grain doses three or four times daily. One of these drugs should be continued for two or three weeks, and then stopped for a week, and resumed for perhaps two weeks, then stopped for a week, and so on. The sedative mixture may be discontinued when the patient ceases to have too much consciousness of the heart beat, or if the blood-pressure comes down toward a more normal figure. The quinidin should be continued for perhaps a week, and if it does not influence the frequency of the arhythmia it should be discontinued and digitalis prescribed in its place, giving at the start 4 grains daily for four days, and then continuing with 3 grains daily for two or three weeks. Usually the quinidin will control an arhythmia due to premature beats, but if it fails digitalis is worth a trial.

This patient should be told not to exert himself enough to bring on this palpitation of which he complains. He should walk no more than he can help, and he should not do any heavy exercise, such as lifting, and not much stair climbing.

In preparation for his antisyphilitic treatment he should have his mouth carefully gone over by a dentist and the teeth cleaned, and other needed repairs made. It is best to start these patients with a course of mercury and iodid. If this is done there is very little chance for a bad reaction when the arsenical drugs are used. When starting the treatment with arsenic bad results have been reported, and it is our feeling that these are almost entirely avoided when mercury is used

first. After ten days or two weeks, when we have been able to judge how much our medication will control the patient's symptoms, we should start in with the antisyphilitic treatment, giving him mercury by injection, 1 grain of the salicylate every five to seven days, and potassium iodid by mouth, 10 or 15 grains, three times daily. This treatment should be continued until he has had twelve mercury injections, and then he may be allowed to rest ten days before further treatment.

He should then have a course of neosalvarsan injections. The first dose should be 0.15 gm., and if no unpleasant reactions occur later doses should be 0.45 gm. or even 0.6 gm. The patient should be given a total of nine injections of neosalvarsan at intervals of about a week, and following this the treatment may again be suspended for about ten days. Alternating doses of mercury and salvarsan should be given until the Wassermann becomes negative, or until three courses of each have been given, with the Wassermann still remaining positive. In such a case bismuth should be tried; given by intramuscular injections, preferably in the form of potassium bismuth tartrate, starting with $1\frac{1}{2}$ grains, giving weekly injections and increasing the dose by the third week to 3 grains each time. If the Wassermann is still positive a longer rest from the medication should be given, and then a course of bismuth, followed by a course of arsenic.

Patients with cardiovascular syphilis sometimes develop alarming symptoms rather suddenly, which are for the most part due to obstruction of the mouths of the coronary arteries by luetic pathologic processes. These attacks must be distinguished from anything that might be considered as a bad reaction to the salvarsan or other antisyphilitic drug. Some authors feel that it is dangerous to give salvarsan to these patients on account of the possibility of serious cardiac attacks; personally I feel that these attacks are part of the disease, and I have never seen any occurring in these patients during the administration of salvarsan which I was really able to attribute to a specific effect of the drug.

Case III.—The third case which I will show you is a man sixty-five years of age, who for five or six years had been subject to

occasional attacks which would come on for no apparent reason. There was a heavy precordial discomfort with a sense of palpitation and a feeling of weakness; this would last from one-half hour to two hours, and would then pass off. Otherwise he feels quite well and is rather active. He plays golf, and is able to walk three or four miles without any special shortness of breath, although hills do force him to go slowly for this reason. At first the intervals between attacks would be as long as three or four months, or even eight or ten months, but of late the attacks have come as often as once in four or six weeks. He has a slight chronic cough without any expectoration. The bowels are normal. He is not especially troubled by shortness of breath. He has had no sicknesses since childhood and denies venereal infection.

The examination shows a man appearing about sixty-five years of age, showing no pallor and no cyanosis. His eyes show a definite arcus senilis. The peripheral arteries are somewhat thickened, the pulse rate is 72 per minute, the rhythm is irregular due to the occurrence of occasional premature beats; the area of cardiac dulness extends 13 cm. to the left of the midline, which is 3 cm. beyond the midclavicular line. The apex impulse is somewhat increased in force; the first heart sound at the apex is normal. At the apex there is a long, harsh systolic murmur following the first heart sound. The aortic second sound is slightly accentuated and has a somewhat ringing quality. There is a rather faint, harsh, systolic murmur, with its maximum at the aortic area, and a very faint, long, blowing diastolic murmur heard here and also in the fourth left intercostal space at the border of the sternum. The blood-pressure was 145/55. The lungs were negative except for a slight degree of emphysema. There was no edema of the extremities. The *x*-ray outline of the heart is shown in Fig. 137. The ventricular area is not definitely enlarged, although it is at the upper limit of normal. The transverse diameter of the heart was 13 cm. and that of the chest 27 cm. The outline of the aorta is definitely enlarged and there is an appearance of tortuosity which is much more definite in the oblique views than in the anteroposterior direction. This is an appearance commonly seen in patients who have

Fig. 137.—Orthodiagraphic tracing of third patient.

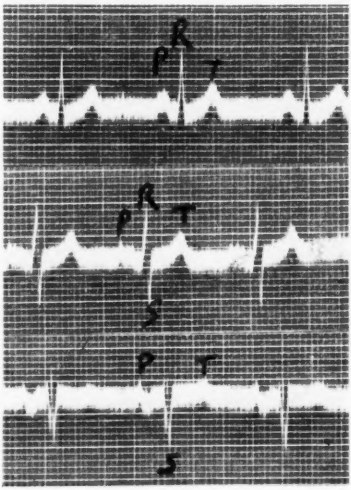

Fig. 138.—Electrocardiogram of third patient showing no significant abnormality except left axis deviation.

atheromatous changes in the wall of the aortic arch. The electrocardiogram shows a normal rhythm, interrupted by occa-

sional auricular premature beats. The auriculoventricular conduction time is normal, P-R measuring 0.18 second. The QRS group shows neither right nor left axis deviation and there is no abnormality of QRS or of T to suggest the presence of myocardial disease. The Wassermann reaction was reported negative.

This patient also has aortic insufficiency and evidences of atheromatous changes in the aortic arch with some dilatation of the aorta. The arch is not definitely enlarged. The electrocardiogram does not show any evidence of myocardial degeneration. The premature beats and the spells of palpitation of which the patient complains are probably related. The premature beats arise in the auricle and denote an irritability of an area of muscle there, so that it is quite possible that the spells of palpitation are due to short paroxysms of auricular fibrillation or of auricular tachycardia. This arhythmia is of comparatively recent appearance and may well depend upon areas of the auricular musculature not receiving a proper blood-supply on account of arteriosclerosis of the coronary arteries. The systolic murmur at the apex can likewise be explained on a functional basis, for the muscle of such a person would not have its normal tone and accordingly might not support the valve orifice properly during systole, so that its proper functioning would be prevented. There is probably no disease of the mitral valve, but simply a mitral incompetency due to mitral dysfunction. It is even possible that this dysfunction has a basis in deficient blood-supply due to coronary arteriosclerosis, and there may even be a small amount of myocardial degeneration in the muscle. The normal appearance of the electrocardiogram would suggest, however, that this myocardial degeneration, if present, is but slight in extent.

What now is the etiology of this patient's disease? There is nothing in the history or the examination to suggest that the patient has ever had rheumatic or syphilitic infection. There is considerable to suggest that the root of the aorta is involved in a moderately advanced arteriosclerotic process, and it seems likely that this patient has aortic insufficiency because the atheroma has involved the flaps of the aortic valve itself. The

etiology then is arteriosclerosis, which by involving the root of the aorta has caused the aortic insufficiency, and by involving the coronary arteries has given rise to the arhythmia.

The regulation of this man's exercise and diet is quite analogous to that outlined for the patient with syphilitic heart disease, except that in this man the limitation of effort is less; he need be scarcely at all restricted in his physical activity. He is not overweight, so his diet need not be restricted. The bowels do not need any medical attention. The annoying symptom at present is the palpitation, which comes in attacks. For the relief of this he should be given a capsule of quinidin sulphate, 4 grains three times daily. Since he has arteriosclerosis of the coronary arteries he should be given either metaphyllin or theocalcin as it was to be given the syphilitic patient. Here again we may expect to bring about some improvement in the blood-supply in certain areas of the myocardium, the arteries to which have been narrowed. These drugs dilate the more healthy collateral branches and thus bring in by other channels the needed blood. One of these drugs should be given about half the time, perhaps taking one for ten days and then omitting it for ten days. If they have any such effect as we ascribe to them, they should be continued for a considerable length of time in order to correct such a pathologic lesion as must be present. The use of potassium iodid in such a patient is certainly problematical. We do not feel that there is any syphilitic feature in this case, but many of these patients seem to do very well when taking relatively small doses of potassium iodid. Such a dose as 10 grains of potassium iodid twice daily will scarcely ever be enough to upset a patient, and sometimes it seems to have a beneficial result symptomatically. This patient should therefore be put on this dose for two or three weeks, and then the drug should be discontinued and the patient watched for a return of the symptoms.

In summarizing the features of these patients it has been most interesting to note how similar have been their symptoms, and how similar the physical findings, and yet, owing to the difference in the etiology, the treatment in each case is quite

different. We do not, of course, intend to imply that it is only recently that we have realized that different forms of heart disease have a different etiology, but it is only recently that we have fully appreciated how the type of the pathologic changes depends upon the etiologic factor. For this reason the diagnosis of the etiologic factor is even more important than the diagnosis of the pathologic condition. In considering the treatment of these patients we miss a great opportunity for therapeutic achievement if we are content to only treat the cardiac disease, or the results of this disease which have given rise to the cardiac dysfunction. Our therapeutic aim must be not only to treat the disease but also to treat its cause, and by so doing to check its progress.

CLINIC OF DR. SAMUEL BROCK

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NEUROLOGIC CLINIC: (*A*) TWO UNUSUAL CASES OF PAROSMIA. (*B*) AN UNUSUAL CASE OF SUBDURAL HEMATOMA. (*C*) ANEURYSM OF THE INTRACRANIAL PORTION OF THE LEFT INTERNAL CAROTID ARTERY[1]

DISTURBANCES of the olfactory function as outstanding symptoms in neural disease are uncommon. This is rather surprising in view of the wide distribution of pathways subserving this function in the brain. However, it is due to two facts: first, the development of the forebrain in man, the psychic functions of which supersede the simpler function of smell, allocated to the rhinencephalon; second, disturbances in the function of smell are oftener due to abnormalities in and about the nasal mucous membrane and come within the sphere of the rhinologist. The two following cases are of unusual and especial interest because of the annoying symptoms referred to this sense.

Case I.—S. L. is a single male, twenty-six years old, of Belgian birth. His present illness began fifteen years ago (1913). He became subject to peculiar attacks in which he experienced an odd "unbearable" thought, a strange odor, a difficulty in speech, which consisted of a fumbling after words, and some obscuration of consciousness. These symptoms passed over quickly and were followed by yawning and a slight transient weakness. The seizures were regarded as uncinate fits belonging to the petit mal category. They varied in frequency from one in ten weeks to eight in one day. Some of them were associated

[1] I am indebted to Dr. Foster Kennedy, Chief of the Neurological Service of Bellevue Hospital, for permission to report Case III, and to Dr. Paul Stewart, of the United States Marine Hospital No. 70, for permission to report Cases II and IV.

with "queer" acts, such as an impulsive desire to drink water (psychic equivalent episodes). No convulsive seizures occurred until June 13, 1928, on which date he had three grand mal attacks. There had never been any prolonged amnesic periods involving complicated automatic acts. His memory was affected temporarily after the "smell" seizures. The next phenomenon was most unusual and is the cause of the present report. Ever since the grand mal attacks, a matter of three and a half months to the present time, he has suffered from a peculiar disturbance in olfaction. All odoriferous substances are appreciated as a uniform type of sweet odor (parosmia). Nothing is smelled correctly. When given test objects to smell, he was unable to identify diverse substances (coffee, tobacco, etc.), but called them "his odor." Food flavors were somewhat dulled also.

Many repeated examinations of his nervous system were entirely negative. His mental status was quite normal. The urine was normal. The blood Wassermann was negative and *x*-ray examination of the head failed to reveal any evidence of a pathologic lesion.

A beneficial effect was noted on the petit mal seizures by the administration of luminal, gr. $\frac{1}{4}$, sodium biborate, gr. $7\frac{1}{2}$, and nitroglycerin, gr. 1/100, three times daily. Various other combinations had been tried previously.

It is unusual for symptoms to persist between the paroxysms of epilepsy. In this case there is no evidence of gross organic disease, such as neoplasm. However, the peculiar type of seizures first described by Hughlings Jackson as uncinate fits are definitely known to depend upon disturbed function in the olfactory area of the temporal lobe, namely, the uncinate gyrus. From the facts at hand in this case one must conclude that the oft-repeated seizures involving "discharges" from this area of the brain have finally led to slight organic change producing a constant symptom.[1]

[1] It is interesting to note that S. A. K. Wilson has described a similar case on p. 53 (Case No. 1) under the "Psychial Components of Temporal (Uncinate) Epilepsy," in his book, "Modern Problems in Neurology," William Wood & Co., 1929.

Case II concerns a man, J. McV., thirty-five years of age, who was struck by a hand-winch aboard ship on June 8, 1928. He sustained abrasions of the face and lacerations of the forehead, and was unconscious for twenty minutes. At the time he bled profusely from the nose. I first examined him on August 24, 1928. At that time he complained of dizziness and perversion of "taste" and smell. Foods and odors had the same disagreeable "taste" and smell, which he described "like sulphur." The use of various test objects elicited this subjective response. It is interesting to note that the smell of ammonia caused reflex tearing, showing that the trigeminal innervation was normal. The neural examination revealed entirely normal findings except for the above. The absence of any other complaints, and a rather stolid bearing, served to rule out any neurotic factor.

x-Ray examination of the skull late in August, 1928 showed no evidence of fracture or increased intracranial pressure. With the history of epistaxis in mind, and the disturbance of smell as a sequel, I believe we are justified in postulating injury to the olfactory tracts, probably the trigones, superjacent to the cribriform plate of the ethmoid bone. Although unsubstantiated by *x*-ray, I believe there may well have been a fracture of the bone in that neighborhood.

It must be pointed out that the disturbance of "taste" recorded in this case is really a perversion of olfactory function. Flavors that we taste are really smelled; in the strict sense, taste is limited to the perception of sweet, salty, bitter, and acid substances. Hence the frequent loss of the ability to appreciate flavors with coryza, which we loosely consider a loss of taste. In reality it is disturbed smell. Fracture of the skull is followed by many diverse signs. However, parosmia is a rare sequela.

The next 2 cases belong to a different category.

Case III concerns a young male, F. K., nineteen years of age. While boxing on February 17, 1928, he received rather heavy blows on the head, and epistaxis resulted. He stopped after four rounds, vomited, and collapsed in the dressing-room

When examined by a physician, he was found unconscious. The left pupil was constricted and the right fully dilated; neither one responded to light. Artificial respiration and cold applications to the head were employed, and after a half hour the pupils became equal in size and responsive to light. In one hour consciousness had partly returned. He was taken to Bellevue Hospital, and on the day of the injury it was noted that the abdominal reflexes were absent, that there was a Babinski toe sign on the right, and that the lower extremities were somewhat rigid. Inconstant anesthesia of both thighs was noted. He was kept under observation for a number of days, and on February 23d and 24th the following notes were made:

The upper extremities were negative. In the lower extremities there was definite paresis, greater on the left. The abdominal reflexes were more active on the left, but quite exhaustible. The deep reflexes of the lower extremities were overactive, more so on the left, with a tendency to left ankle-clonus. There was a double Babinski toe sign, greater on the left. There were no sensory changes or cerebellar signs. The diagnosis of a subdural hematoma was made, in the neighborhood of the longitudinal fissure, involving the motor leg areas, more marked on the right. On March 1, 1928 a trephining of the skull was carried out under local anesthesia, high up over the right motor area. The dura was found tense and without pulsation. Incision revealed about 25 c.c. of semicoagulated blood, which was removed. Directly after this was done the patient was able to move his paralyzed left leg. Very shortly thereafter he became much brighter mentally. Further improvement occurred, so that he was able to leave the hospital three weeks after operation, walking fairly well, but with some stiffness of the left leg and slight inversion of that foot.

Cases of subdural hematoma have been described by Putnam and Cushing. Essentially, cases of chronic subdural hematoma, of which the above is an example, are characterized by the appearance of signs of increased intracranial pressure, gradually following the receipt of head trauma. Fracture of the skull may or may not be an accompaniment. The localizing signs depend

upon the part subjected to pressure. Recently Ira Cohen (Arch. Neur. and Psych., 1927, 18, 709–723) reports the case of:

"A previously healthy young man who, six weeks after a slight cranial trauma, developed signs of a left cerebral lesion, with increasing papilledema. Operations disclosed a large subdural collection of xanthochromic fluid, a left hemisphere compressed to less than a fourth of its normal size, and a small amount of fluid of the same character beneath the dura of the right hemisphere. During a four months' period the left subdural space was more or less completely emptied nine times and more than 2300 c.c. of fluid was removed. Except for headache and papilledema all signs of disturbed function soon disappeared. The headaches and choked disks were relieved only after a right temporal decompression."

In Cohen's case the subdural accumulation was xanthochromic fluid. In an introduction to Cohen's paper C. A. Elsberg makes the following remarks concerning chronic subdural collections:

"After a cranial trauma, blood, cerebrospinal fluid, or a serous effusion may accumulate underneath the dura and may, after a shorter or longer latent period, give rise to symptoms of disturbed function of the brain. The clinical pictures presented by these patients are often characteristic and similar, but insufficient attention has been directed to the variety of lesions that may be found in the subdural space.

"1. There may be a collection of fluid or clotted blood underneath the dura. This variety is the chronic subdural hematoma recently described by Putnam and Cushing. The blood usually overlies one hemisphere, although it may be found on both sides, and results in more or less marked compression of part of the brain.

"2. Turbid or blood-stained cerebrospinal fluid or a serous exudate may be found under the dura mater over one or both cerebral hemispheres. This is the condition to which Payr gave the name of meningitis serosa sympathetica. In this variety the lesion is essentially an inflammatory one and is secondary to an infection of or actual suppuration in the bones

of the skull or in the tissue of the brain. Unless the primary lesion is relieved the serous fluid may become frankly purulent and a diffuse meningitis may follow.

"3. The subdural space over part of one hemisphere may contain air, or air and fluid, with perhaps air in the substance of the brain, in the arachnoid cisterns and in the ventricles (traumatic pneumocephalus).

"4. The accumulation in the subdural space consists mainly or entirely of cerebrospinal fluid, which may be blood-stained or xanthochromic.

"5. If the condition is unrelieved by surgical therapy the fluid underneath the dura—whether it consists mainly or entirely of cerebrospinal fluid or whether it is a true subdural serous exudate—may finally coagulate and form a more or less solid mass over part of one cerebral hemisphere.

"Subdural collections of cerebrospinal fluid after an apparently insignificant cranial trauma may cause symptoms so similar to those of chronic subdural hematoma that the distinction between the two conditions can be made only at the operating table. The subdural fluid may be blood-stained or xanthochromic; it may be localized over a small area or it may compress a large part of one cerebral hemisphere. Aside from the presence of the large collection of fluid, of a thin fibrinous membrane on the inner side of the dura and of the compressed brain, there are no other gross pathologic changes. The cortex of the compressed brain is normal in appearance, without any evidence of blood-clot or fibrin on its surface."

Case IV.—M. Q. concerns a single white woman of fifty-seven years, who was in good health until September 17, 1928, when she fell forward, and injured her forehead. She was dazed, but not unconscious, and in five minutes had fully regained her senses.

In the middle of 1927 she noticed a small lump on the right side of the front of her neck. Although there seemed to be no symptoms attributable to it, she consulted Dr. Emil Goetsch, of Brooklyn, New York, who operated upon her under general anesthesia. He was good enough to give the following report:

"I found that she had an adenomatous goiter producing definite moderate hyperthyroidism. At operation on March 28, 1928, we found the usual common type of adenomatous goiter containing the characteristic benign nodules. A resection was done of the right lobe, which was the most involved. The left lobe was practically normal. A partial resection was done to this. Examination confirmed our diagnosis of benign adenomatous goiter. Miss Q. made a good recovery with relief of the symptoms of which she complained."

In May, 1928, two months after the operation, the right eye began to "water," and the left one became a little "swollen," teared, and a purulent secretion appeared. Pain in the forehead and a rhythmic "swishing" noise in the head began about the same time.

I saw her for the first time in July, 1928. The following was the clinical picture: Both eyes were proptosed, especially the left. There was marked edema of the conjunctiva of the left eye and congestion of the lower lid with evidence of marked venous congestion. The left scleral veins were full and tortuous. There was ptosis of the left upper lid, and ectropion of the left lower lid (Fig. 139). Slight edema of the conjunctiva was noted on the right. The pupils were small and equal. The right reacted sluggishly to light, the left scarcely at all. There was a fair reaction to accommodation, better on the right. The fundi revealed marked tortuosity of the veins, especially on the left. There was no arterial or venous pulse. On the right there was some circumpapillary choroidal atrophy. The appreciation of color was absent on the left and defective on the right (probably a congenital abnormality). The blind spots were enlarged, and the fields were slightly concentrically contracted. There was homonymous diplopia throughout the field of fixation, and especially on lateral gaze. There was paralysis of the right external rectus muscle. All movements of the left eye were performed with restricted range.

There was no corneal hypalgesia. Sensation on the face was normally perceived. The facial musculature was normal. Hearing was bilaterally diminished due to deafness of the conduction

type. The palate, tongue, and speech were normal. Odors were normally perceived on both sides. There was no tremor of the hands. The reflexes, cerebellar and sensory functions, gait, and station were normal.

Over the entire head a loud systolic bruit was heard. It was also heard in the neck, much better on the left side, but was not audible below the clavicles. The patient also hears this murmur, and complained of it as a "swishing," pulsating tinnitus in both

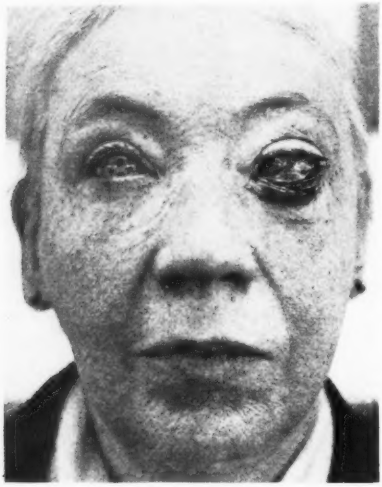

Fig. 139.—Case IV. A case of aneurysm of the intracranial portion of the left internal carotid artery, showing proptosis of the left eye, conjunctival chemosis and ectropion of the left lower lid, left internal strabismus, and ptosis of the left upper lid with overaction of the occipitofrontalis muscle.

ears, which at times takes on a whistling character. *Compression of the left common carotid in the neck causes complete disappearance of the bruit.*

The rest of the physical examination was negative except for (1) a thin, semilunar scar over the suprasternal notch; (2) a heightened blood-pressure, systolic 190 to 200, diastolic 100 to 110; (3) a healed median abdominal scar, running from the umbilicus to the pubis, indicating the site of a previous operation

for fibroma uteri. There were no murmurs to be heard over the cardiac area. The pulse rate was 76. The heart was not markedly enlarged.

The patient was seen again on August 31, 1928, when the following changes were noted: The exophthalmus was less; especially the right eye has receded; the left was slightly less proptosed. Examination of the ocular movements disclosed paralysis of both external rectus muscles. On upward and downward gaze the left eye turned in. The diplopia was the same. The vision on that date was—right, 20/80; left, 20/270. The right eye showed the circumpapillary choroidal atrophy. In the left eye hemorrhage was noted between the disk and macula, and new blood-vessels appeared in the disk. There was no papilledema. While the right eye showed some improvement, vision in the left was deteriorating.

The next examination was on October 2d, when the following notes were made: The patient has gained 8 pounds in the last three weeks (130 to 138 pounds). There is now a distinct external rectus paralysis on both sides, with bilateral internal strabismus. The external rectus paralysis is greater on the right. The other movements are fairly well performed. The fundus of the left eye shows the extreme results of venous stasis in the form of multiple hemorrhages studding the fundus. There is definite new vessel formation on the temporal half of the disk. There is no elevation of the disk. The fields are as last noted. At no time was there any pulsation in the exophthalmic left eye. (I am indebted to Dr. Morris Davidson, ophthalmologist to the Marine Hospital, No. 70, New York City, for the ophthalmoscopic findings in this case.)

The laboratory findings are as follows: Examination of the skull shows no evidence of fracture. There are prominent diploic sinuses and calcification in the pineal body, anomalous but not pathologic. Examination of the chest shows no evidence of pulmonary or pleural pathology.

A diagnosis of aneurysm of the left internal carotid artery is based on the marked systolic bruit heard over the head, and especially on the left side of the neck (being transmitted along

the common carotid artery) and the evidence of venous stasis due to pressure in and about the left cavernous sinus (producing proptosis, the conjunctival chemosis, and venous stasis in the fundus and lids, as has already been described). The aneurysm has produced a modified cavernous sinus syndrome, characterized by external ocular muscle palsy and partial iridoplegia (third and sixth nerve involvement) in addition to the signs of venous stasis on the left side. Evidently circulation in the opposite cavernous sinus was somewhat impeded, as evidenced by the right sixth nerve palsy, and the slight right-sided proptosis. The absence of pulsating exophthalmos speaks against an arteriovenous communication. The recession of the proptosis, especially in the right eye, may reasonably be explained by organization of the clot in the wall of the arterial sac, with a lessening of the pressure effects.

Severe exophthalmos, even dominantly unilateral, may accompany hyperthyroidism. However, this occurs in acute cases with progressive and unmistakable signs of exophthalmic goiter. In this connection the venous hum of the latter disease (bruit de diable) is easily distinguished from the systolic murmur associated with intracranial aneurysm. The absence of signs of hyperthyroidism, viz., the gain in weight, the absence of tremor, the normal pulse rate, and the presence of cranial nerve palsies suffice to rule out this condition.

The absence of any evidence of primary or metastatic malignancy rules out a new growth resting upon the left internal carotid artery, and compressing the cavernous sinus, as a cause of the syndrome.

Of 166 cases of intracranial aneurysm mentioned in Osler's "Principles and Practise of Medicine," 10th ed., 1925, 49 occurred in the middle cerebral, 44 in the basilar, and 24 (or 14 per cent.) in the internal carotid artery. The rest of the aneurysms occurred in various other cerebral arteries.

Having settled upon the diagnosis of aneurysm, it becomes necessary to determine the cause thereof. It is a well-known fact that intracranial aneurysms are not as often luetic as aneurysms in other parts of the body. In discussing the etiology

of intracranial aneurysm Osler speaks of: (*a*) Congenital defects; (*b*) endarteritis, simple or luetic; (*c*) embolism (particularly emboli arising from cardiac valves during the course of ulcerative bacterial endocarditis). The emboli lodge in the wall of a vessel, cause inflammation and subsequent weakness of the vessel wall and aneurysmal dilatation. To these aforementioned causes must be added cranial trauma, especially in the case of the internal carotid artery. In the literature on so-called "pulsating exophthalmos" there are numerous instances recorded of trauma inducing aneurysm of this vessel. Recently trauma has again been described as a cause of aneurysm of the internal carotid artery in the report of J. L. Birley (Brain, 51, 1928, 184–208). He gives a detailed description of an interesting case following fracture of the base of the skull.

In the absence of signs of lues, and with a history of trivial trauma occurring in an individual with hypertension and arteriosclerosis, I feel that the weight of evidence favors degenerative disease of the blood-vessels as the true cause of this aneurysm.

Treatment.—The treatment of aneurysm of the internal carotid artery is based largely on experiences gained in cases of pulsating exophthalmos. In recent years the subject has been discussed by G. B. Rhodes (Ann. of Surg., April, 1916, pp. 389–414) and later by C. E. Locke (Ann. of Surg., July, 1924, pp. 1–24). To these two articles one is referred for statistical and therapeutic details.

Briefly, the treatment is surgical and consists mainly of ligation of the internal carotid, the external and internal carotid, or the common carotid artery of the same side in the neck. The two great dangers attending the operation are: (1) The results of cerebral anemia, which causes a hemiplegia on the opposite side of the body, and aphasia in cases of left-sided ligation; (2) an extension of thrombosis from the site of the ligature, with the danger of fatal embolism. Locke emphasizes the necessity for a course of carotid compression lasting one or more weeks before operation, and the application of a looser ligature than is commonly used in vessel ligation.

I am privileged to have the opinion of Dr. G. B. Rhodes

(whose able report was above cited). After examination of this woman he believes that a ligature operation is indicated in view of the disappearance of the murmur, when the left common carotid artery is compressed in the neck. This speaks against the establishment of a strong collateral circulation, the presence of which would preclude a favorable operative result.

CLINIC OF DR. HERMAN ELWYN

GOUVERNEUR HOSPITAL

THE DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF NEPHRITIS

THE term "nephritis" as we use it at the present time covers a number of different affections of the kidneys. These individual forms of nephritis are distinct entities clinically and pathologically, and, in some forms, also etiologically. Prognosis as regards recovery and duration of life is different with each individual form of nephritis. When we meet, therefore, a symptom which calls attention to the kidneys, such as albuminuria or edema, the question of diagnosis is twofold: (1) Is the patient suffering from nephritis? and (2) if nephritis is present, what is the particular form? To answer these questions properly we must know the meaning of the symptoms which are found in the various forms of nephritis, the disturbance in function of the kidneys, and we must be able to correlate these with the pathologic process in the kidneys. Our discussion resolves itself, therefore, into a consideration of the individual symptoms found in nephritis, disturbance in function of the kidneys, and the extent to which these are found in individual forms of nephritis.

Symptoms of Nephritis.—The symptoms which occur in nephritis are of two kinds: (1) The urinary symptoms which are the direct result of the damaged kidneys, namely, the presence of albumin and casts in the urine, the presence of blood in the urine, and the changes in the daily amount of the urine. (2) Symptoms which are only indirectly related to the kidney damage, namely, edema, increase in blood-pressure, convulsions, and changes in the eye-grounds.

The manner in which these symptoms are produced is not at all clear in every instance, but in many instances their connection with certain pathologic changes in the kidneys is very definite. Hematuria occurring in nephritis is a definite symptom of damage to the glomeruli and indicates the presence of an acute inflammatory process in them. It is the one symptom which indicates the presence of an acute glomerulonephritis, provided surgical diseases of the kidneys and the rest of the urinary tract and other constitutional diseases which cause bleeding are excluded. In the course of chronic nephritis the appearance of hematuria indicates the recurrence of an acute process in the glomeruli. The blood is derived from the ruptured capillaries in the glomerular tuft.

Albumin in the urine occurs in every form of nephritis and is, therefore, by itself not indicative of any particular lesion in the kidneys. It is always derived from the proteins of the blood plasma which have passed through the glomerular filter. It is, therefore, really indicative of a damage to the glomerular capillaries and the parietal layer of Bowman's capsule. Such a damage may, however, be very slight and not be shown histologically. A temporary retardation of the venous flow, pressure on the renal artery, febrile conditions, and many other conditions which interfere only slightly with the oxygen supply to the cells of the glomeruli cause sufficient damage to them to permit the proteins of the blood plasma to pass through.

Although the presence of albumin is by itself not indicative of any particular form of nephritis, the quantity of albumin has some significance. Large quantities of albumin are found, especially in certain cases of nephritis which are characterized at the present time as lipoid nephrosis.

Whenever albuminuria alone is found the question whether it is present only when the individual is up and about and disappears on lying down, that is, whether the albuminuria is an orthostatic one, must be settled. An orthostatic albuminuria is not indicative of nephritis, but is found in young people inferior constitutionally, and is frequently accompanied by a marked lumbar lordosis.

Hyaline and granular casts have the same significance as albuminuria. Blood casts have the same significance as hematuria, and cellular casts indicate destruction of the renal tubules.

The daily amount of urine may be increased, or it may be diminished, even to complete suppression—anuria. The water in the urine is derived from the blood by the passage of a deproteinized plasma through the glomeruli. A diminution or complete suppression of urine formation indicates that the plasma of the blood does not reach the glomerular filter at all or reaches it only in insufficient quantities. This is necessarily the case when the glomeruli are extensively inflamed, and oliguria and anuria are therefore symptoms of an acute diffuse inflammatory process in the glomeruli. The water of the blood plasma may, however, be prevented from passing through the glomeruli in sufficient amounts even when the latter are not diseased. This occurs when all the small arteries are contracted, as in reflex anuria from a stone in the ureter. It also occurs when certain conditions outside of the kidneys are responsible for the blood plasma reaching the glomeruli in insufficient amount. This is the case in high intestinal obstruction.

An increase in the amount of urine when due to a disease of the kidneys indicates that although a sufficient amount of water is passing through the glomeruli, reabsorption in the tubules is diminished. This occurs when the number of the tubules in the kidneys is reduced. Such a reduction is chiefly secondary to a destruction of the glomeruli belonging to these tubules. Polyuria when of renal origin is thus a symptom indicative of a chronic destruction of the glomeruli and tubules and occurs in the course of chronic glomerulonephritis.

Of the indirect symptoms we have to consider edema and hypertension. The manner in which these symptoms are produced has been subject to a good deal of speculation and is not at all clear. We know, however, that both of these symptoms occur in certain forms of nephritis, and that in all probability renal and extrarenal factors are concerned in their production.

We have learned to connect the presence of edema in renal diseases (1) with acute nephritis, when all the glomeruli are

inflamed in a diffuse manner; (2) with the subchronic and chronic forms of nephritis; (3) as part of the symptom-complex of lipoid nephrosis.

We have learned to connect the presence of an increased blood-pressure (1) with acute nephritis, when the glomeruli are inflamed in a diffuse manner; (2) with a chronic inflammatory process in the glomeruli—subchronic and chronic glomerulonephritis; and (3) with diseases of the small arteries and arterioles of the kidneys—renal arteriolosclerosis.

The other symptoms previously mentioned are convulsions and retinal changes. Convulsions in nephritis are always preceded by a sudden rise in blood-pressure. This is especially apt to occur in acute diffuse nephritis and convulsions are, therefore, most frequent in this form. They occur occasionally in the terminal stage of chronic nephritis.

The changes in the eye-grounds are commonly summarized under the term "albuminuric retinitis," but are more aptly characterized by the term "hypertensive retinitis" or "hypertensive retinal changes." They consist of swelling of the optic disk, narrow arteries, congested veins, hemorrhages, irregular white cotton wool patches in the retina, and small whitish deposits arranged in radiating lines around the macula. These changes are the result of maximal contraction of the arteries and occur in prolonged extreme hypertension. They are, therefore, found especially in chronic glomerulonephritis and in the malignant form of renal arteriolosclerosis, especially toward the terminal stage.

We have thus summarized the individual symptoms which occur in nephritis and turn now to a consideration of disturbances in function.

Disturbance in Kidney Function.—The consideration of disturbances in kidney function involves an understanding of what the normal kidney does. The function of the kidneys is: first, to excrete the waste products of protein metabolism, chief of which are urea, uric acid, and creatinin; second, to help maintain the normal volume and composition of the blood by keeping back those substances which the body needs, such as water,

salt, and sugar, and by excreting these substances when they are present in the blood in excess; and third, to help in the neutrality regulation of the body by excreting any excess of acid or base. When water is present in the body in excess the waste products are excreted in a very dilute solution; when water is withheld, these substances are excreted in a very concentrated form. By measuring the ability of the kidneys to excrete these substances in a dilute or concentrated form we measure the functional ability of the kidneys. The ability of the kidneys to concentrate the urine can be measured by taking the specific gravity of the urine. With healthy kidneys this rises to 1.030 and 1.036 when the intake of water is withheld. The ability of the kidneys to dilute the waste substances can be measured by the administration of a single large amount of water, 1000 or 1500 c.c. When such an amount is taken in the morning on an empty stomach by a healthy person, it is eliminated within two and a half to three and a half hours, and the individual portions reach to 200 and 300 c.c., with a low specific gravity. Both of these tests, the concentration and the dilution test, are best performed together in the following manner:

The patient is given 1000 c.c. of water in the morning and the urine examined for the total amount and its specific gravity every hour for four hours. The patient is told not to take any fluid during the rest of the day and the urine is collected and examined for its total amount and its specific gravity every two hours during the day, and again in the morning. The largest half hourly or hourly individual portion after the ingestion of the water, and the time it takes for the whole amount to be excreted, measure the diluting power of the kidneys. The highest specific gravity of the urine obtained in an individual portion during the twenty-four hours measures the ability of the kidneys to concentrate the urine.

These tests are interfered with by the presence of an excess of fluid in the body, especially by the presence of edema. The water ingested is then apt to be shunted off into the edema fluid and thus does not reach the kidneys. Depriving the patient of water is apt to mobilize the edema fluid, which enters the blood-

stream, reaches the kidneys, and interferes with the concentration test.

It is the function of the glomeruli to let the excess of water pass through their capillaries, and so produce a dilute urine. With the destruction of the glomeruli this function is diminished in proportion to the extent of the destruction, and the time of excretion is prolonged. Concentration is a function of the tubules, but with the destruction of the glomeruli the corresponding tubules also disappear, and with a diminution in their number the function of concentration is diminished. With the dilution and concentration tests we are able to measure the extent of the loss of the functioning tissue in the kidneys.

When this loss reaches a certain extent the waste substances in the blood cannot be eliminated, and we then find an increase in the blood above the normal of the total non-protein nitrogen, and of urea, uric acid, and creatinin. Such an increase may also occur when the damage to the kidneys is not very extensive by the ingestion of a large amount of protein, and a reduction in the intake of protein is then followed by a diminution in the level of the waste substances in the blood. When the reduction of the protein intake to a minimum does not result in a diminution of the increased amount of the total non-protein nitrogen in the blood, and of the urea, uric acid, and creatinin, then we know that the function of the kidneys, that is, their ability to excrete the waste substances, is diminished to such an extent that the danger of poisoning by these waste substances—uremia—is imminent. With such kidneys the specific gravity of the urine is practically fixed at about 1.010 or 1.012, and the ability to concentrate further is entirely lost.

We have thus as a means of measuring the functional disturbance of the kidneys the dilution and concentration tests, and the determination of the amount of the waste substances in the blood.

As an additional test of the functional capacity of the kidneys we have the phenolsulphonephthalein test, the value of which has been definitely established.

It remains for us to see to what degree the symptoms and

functional disturbances appear in the individual forms of nephritis. To establish a diagnosis of nephritis is not at all difficult when several of the symptoms are present. When albuminuria, hematuria, edema, and hypertension are found, the diagnosis of nephritis is obvious. It is much more difficult when only albuminuria alone, or when hypertension alone, is found. We must then investigate the functional capacity of the kidneys to see whether any diminution in function is present.

The Individual Forms of Nephritis.—We divide the various diseases which are comprised under the term "nephritis" or Bright's disease into three classes: (1) Those which affect primarily the glomeruli and are of an inflammatory character, and in which the tubules are secondarily affected as a result of the damage to the glomeruli—the glomerulonephritides; (2) certain forms in which the tubules are predominantly affected and in which the glomeruli do not show any gross histologic changes—tubular degeneration or, as it is now called, nephrosis; and (3) in which the small arteries and arterioles are primarily affected—renal arteriolosclerosis.

The inflammatory diseases of the glomeruli—the glomerulonephritides—constitute the most important group and occur as acute or chronic forms The one symptom which characterizes all the acute forms is the hematuria. The diagnosis of the particular form of acute nephritis under observation is dependent upon the presence or absence of other symptoms and of certain etiologic factors.

In the embolic focal nephritis hematuria is the only symptom indicative of an inflammatory process in the glomeruli. In this disease the lesions in the glomeruli have an irregular focal distribution and in each glomerulus only a few loops are affected. The rest are able to carry on the work of the kidney. There is, therefore, no disturbance in renal function, no increase in the amount of the waste substances in the blood, no edema, no hypertension, and no change in the dilution and concentration ability of the kidneys. This disease occurs only in the course of subacute bacterial endocarditis due to the Streptococcus viridans, and has, therefore, a distinct etiology. The presence of hematuria

in the course of this form of endocarditis is sufficient to establish the diagnosis.

In the non-embolic focal nephritis hematuria is also the only symptom, in addition to the albuminuria, indicative of the disease. Here also the lesions in the glomeruli, although not embolic, have a focal distribution. Many glomeruli are not affected and in the diseased glomeruli only a number of capillary loops are affected, while the others are free to perform their normal function. There is no edema, no hypertension, no disturbance in renal function. This disease is quite common and occurs in the course of acute tonsillitis, pharyngitis, and infections of the upper respiratory tract generally; also in the course of erysipelas, of wound infections, and in the first week of scarlet fever. The organism which is responsible for the focal nephritis is the hemolytic streptococcus, and in many cases this organism has been recovered from the urine. Other organisms may be responsible. The occurrence of hematuria in the course of the above-named infections, with the absence of other renal symptoms, especially of edema and of hypertension, establishes the diagnosis and differentiates this disease from acute diffuse nephritis. The disease is apt to recur frequently and become chronic. The eradication of the focus of infection in the upper respiratory tract is often followed by a sudden increase in the hematuria, and sometimes by a cure.

In acute diffuse nephritis practically all the glomeruli of both kidneys are uniformly involved. They are bloodless, swollen, and filled with cellular elements which present a hindrance to the flow of blood through their capillaries. There is, therefore, in addition to the hematuria and the albuminuria a diminution in the amount of urine, in some of the severe cases even to complete anuria. There is edema, and an increase in blood-pressure which may reach only to 140 or 150 mm. of mercury, but which may also reach to over 200 mm. Kidney function is disturbed and there is an increase in the amount of the waste substances in the blood. Depending upon the severity of the disease, the non-protein nitrogen in the blood may reach 70 to 100 mg. per 100 c.c. and more, and the urea nitrogen 50

to 80 mg. and more. When there is anuria the figures become extremely high. The dilution and concentration tests are of little value in acute diffuse nephritis, as the diminution in the output of urine is obvious and disturbance in kidney function is apparent from the chemical examination of the blood. Convulsions are a frequent complication in this form of nephritis. The eye-grounds show a variable swelling of the disk and narrow arteries, but these are not found in all cases. The disease occurs typically as a sequel of scarlet fever and appears ordinarily about nineteen to twenty-one days after the onset of the disease. It also occurs following an acute throat infection, usually one or two weeks after the onset of the infection. A third factor is exposure to cold and wet and the nephritis may then appear within a day or two.

So much for the diagnosis of the acute nephritides.

In the diagnosis of subchronic and chronic forms we must have an understanding of what the pathologic process in the kidney is. These forms begin as an acute diffuse nephritis. The acute process subsides and is then followed by a gradual hyalinization of the capillary loops in the glomeruli and the gradual obliteration of the glomeruli. With the destruction of the glomeruli the corresponding tubules also disappear. The destruction eventually reaches an extent where the remaining glomeruli are insufficient to perform even the minimal function of the kidneys, and uremia results. This process of hyalinization and obliteration of the glomeruli may culminate in a short period, or it may stretch over years, even twenty-five years. In addition these patients are subject to recurrent attacks of acute nephritis, which complicates the clinical picture.

In these forms of nephritis there is often a long period in which kidney function is very little impaired and there is no increase in the amount of the waste substances in the blood. In this period the patients present one of two clinical pictures. In one, there is marked albuminuria, edema, and either a normal or a moderately increased blood-pressure. The dilution and concentration tests are difficult to carry out because of the edema. When tested in an edema-free stage a diminution in

kidney function is found, depending upon the degree and the progress of the disease. The non-protein nitrogen and the urea in the blood are normal in amount, but there is frequently found a diminution in the proteins of the blood plasma due to the loss of albumin, and an increase in cholesterol. This picture may last for many years, but eventually hypertension becomes marked, and later uremia supervenes.

The second clinical picture is dominated by hypertension in addition to a varying degree of albuminuria. For a long period these may be the only symptoms, and the question frequently arises whether we are dealing with this form of chronic nephritis or with the benign hypertension of renal arteriolosclerosis. The following elements help to differentiate the two conditions. In chronic nephritis we frequently obtain the history of an acute diffuse nephritis following scarlet fever or a throat infection; the albuminuria is more marked; the diastolic pressure is much higher as compared to the systolic pressure than in benign hypertension; the dilution and the concentration tests show a definite diminution in the functional ability of the kidneys in chronic nephritis and practically none at all in benign hypertension; the patients look pale in chronic nephritis, the "white hypertension" cases of Volhard, and there is frequently found a considerable anemia when the blood is examined. In benign hypertension the patients look full blooded, the "red hypertension" cases of Volhard; and there is no anemia. On the contrary, a slight degree of polycythemia is occasionally found. The further course of the disease helps to differentiate the two conditions, the benign hypertension remaining stationary, while the cases of chronic nephritis progress downward to an increasing renal insufficiency and to uremia.

Both of these clinical pictures may be found combined, that is, marked albuminuria, marked edema, hypertension, with varying degrees of diminution of kidney function, may be found together. In such cases the diagnosis of chronic nephritis presents little difficulty.

Eventually, after a few or many years, the case of chronic nephritis passes into the terminal stage. This is characterized

by the permanent inability on the part of the kidneys to excrete the waste products of protein metabolism. The waste substances accumulate in the blood and we find the total nonprotein nitrogen, and the urea, uric acid, and creatinin increased. The ability of the kidneys to dilute and concentrate the urine is lost, and we note that the specific gravity of the urine is fixed at about 1.010. There is a variable amount of albumin in the urine; there is hypertension and cardiac hypertrophy, and a considerable degree of anemia. The diastolic pressure is especially high, reaching 140 to 160 mm. of mercury, while the systolic pressure varies around 200 to 240. Higher and lower figures occur. The eye-grounds show all the changes which we have previously mentioned. Pericarditis is a frequent complication.

With this clinical picture the diagnosis of the terminal stage of renal insufficiency is obvious. It is not so easy, however, to determine whether we are dealing with the end stage of chronic nephritis or with the end stage of malignant sclerosis. This brings us to a brief consideration of renal arteriolosclerosis.

Renal Arteriolosclerosis.—Arteriosclerosis of the renal artery and its larger branches is a frequent pathologic finding in old people. It does not produce any renal symptoms and is of no significance clinically. Arteriosclerosis of the small arteries and arterioles—arteriolosclerosis—is of great significance clinically and occurs very frequently. The arterioles which are affected become narrowed and here and there the lumen becomes completely closed. Wherever this happens the glomeruli supplied by such arteries and arterioles do not receive any blood. They collapse, become surrounded by connective tissue, and are finally completely obliterated. The corresponding tubules also disappear. The process of development of arteriolosclerosis is an extremely slow one, and in most cases, in spite of the disappearance of many glomeruli, does not reach a stage where renal function is impaired to any considerable degree.

The clinical picture of this disease presents itself under the syndrome of hypertension. The hypertension develops gradually, and becomes permanent at about the fifth decade. It passes under the name of benign hypertension, or of essential

hypertension, or of renal arteriolosclerosis without renal insufficiency. A trace of albumin occasionally occurs, but there is no loss of renal function. The dilution and concentration tests give normal results and there is no increase in the waste substances in the blood. The changes found in the retina are those of arteriosclerosis, namely, tortuous arteries, congested veins, and indentation of the vein where it is crossed by an artery. Hemorrhages in the retina also occur.

The course of this disease is a benign one as far as the kidneys are concerned. It may last many decades, and death is usually due to diseases of the coronary arteries of the heart, or as a result of arterial diseases of the brain. Benign hypertension must be differentiated from chronic nephritis during the stage of permanent hypertension when renal insufficiency is still very slight. The absence of any renal insufficiency, of anemia, of an excessively high diastolic pressure, of the history of an acute nephritis, its presence in more elderly people, the comparatively slight amount of albumin or its complete absence, the absence of extremely narrow arteries in the retina, serve to distinguish the benign arteriosclerosis from chronic nephritis.

There are, however, certain cases of renal arteriolosclerosis which do not run a benign course. In these cases the arterial changes begin much earlier in life, as early as the second and in some rare cases even the first decade. In addition to the changes in the small arteries and arterioles characteristic of arteriolosclerosis there are found, in a focal distribution, inflammatory changes in the intima of these vessels and necrotic changes in their walls, an arteriolitis and arteriolonecrosis. Many of the afferent arteries of the glomeruli become occluded and this is followed by the collapse of the glomeruli and their disappearance, and with them the disappearance of the corresponding tubules. Other glomeruli show the same process that is seen in the arterioles, with a certain amount of inflammatory reaction. Some of the glomeruli are normal in appearance. This form of renal arteriosclerosis, so well studied by Fahr, is generally known at the present time under the term of "malignant sclerosis" or under the term "renal arteriolosclerosis with renal insufficiency." It

was formerly included under the term "primary contracted kidney."

Clinically this disease presents the symptoms of hypertension for a long time, just as the benign form. The patients are usually younger. The blood-pressure is higher, especially the diastolic. Systolic readings vary up to 200 and 300 mm. of mercury, and diastolic figures of 140 to 170 mm. are observed. Albuminuria occurs and is variable in amount. The loss of glomeruli and tubules soon leads to renal insufficiency, and the clinical picture is now the same as that of the terminal stage of chronic nephritis. Diminution of the dilution and concentration ability of the kidneys, fixation of the specific gravity of the urine at around 1.010 or 1.012, increase in the total non-protein nitrogen, and the urea, uric acid, and creatinin in the blood are found. All the eye changes which are characteristic of the terminal stage of chronic nephritis are also found in this disease.

The diagnosis between these two conditions, between the terminal stage of chronic nephritis and malignant sclerosis, that is, between the secondary and the primary contracted kidney, is difficult and frequently impossible. When the history of an acute nephritis following scarlet fever or following an acute tonsillitis is obtained, or when recurrent attacks of acute nephritis are observed, the diagnosis of chronic nephritis in the terminal stage is definite. When such a history cannot be obtained and recurrent attacks of acute nephritis are not observed, the diagnosis between the two conditions is practically impossible. When the case has been followed for a long time, from the period of hypertension without any renal insufficiency to the development of the insufficiency, the diagnosis of malignant sclerosis may be made. Unfortunately, the exact differentiation between these two conditions is at this period of no practical importance. For both represent end stages, and when the waste substances in the blood remain permanently high, the fatal outcome is within sight.

There remain for us to discuss the tubular degenerative diseases or the nephroses.

Slight tubular degeneration occurs in many conditions, espe-

cially in fever, and is accompanied by a mild albuminuria. This hardly deserves the name of a renal disease. The predominantly tubular degeneration which is of importance is lipoid nephrosis.

Lipoid nephrosis, when it occurs alone, is a rare affection. It occurs more frequently in the course of chronic nephritis, in that form which runs for a long period with marked albuminuria and with marked edema. It also occurs in combination with amyloid disease. When occurring alone lipoid nephrosis presents a definite symptom-complex which easily separates it from other diseases of the kidneys. There is marked albuminuria and marked edema. There is no hypertension, no cardiac hypertrophy, no increase in the waste substances in the blood. The ability of the kidneys to concentrate is normal as shown by the high specific gravity of the urine when the albumin is filtered off. Doubly refractive granules are found in the urine on microscopic examination. The blood examination reveals a diminution in the total proteins of the blood plasma from the normal 7 to 8 per cent., to as low as 5 or 4 per cent., and even lower. The reduction is in the albumin fraction, the globulin remaining normal or being actually increased. There is an increase in the cholesterol of the blood from the normal of 0.175 to 0.225 per cent. to as high as 0.400, 0.600, 0.800 per cent. and more.

When this symptom-complex is present the diagnosis of lipoid nephrosis is definite. Whether this condition is present alone or whether it is present as a transitory stage in the course of chronic nephritis can only be determined after prolonged observation. The appearance of hypertension and of renal insufficiency indicates that chronic nephritis is present.

CLINIC OF DR. WINFIELD SCOTT PUGH

CITY HOSPITAL

BLOOD IN THE URINE

IT has recently been asked of us, Why do you keep pounding on the subject of bloody urine? Continuing, our good friends say, Everyone, in this enlightened age, is aware of its dire significance. Ah, would that this were true! Unfortunately we are still seeing cases presenting as their chief symptom blood in the urine, some having gone for months without a definite attempt being made to find its cause. Only recently there came to us a man who had been receiving ergot and calcium lactate for six months to check the loss of blood in the urine. Examination revealed a tumor in the bladder. Within a fortnight we were called to see a little tot of seven years who was passing bloody urine. She was, according to reports, a chronic bed wetter. In the last three months blood was noted in the urine. This, a physician believed, to be due to a urinary irritation. Recently the parents became alarmed and the child was seen by us in consultation. The end-result of our findings was a left nephrectomy for a unilateral tuberculosis. I am well aware that the expression "criminal neglect" is in the nature of a severe indictment, nevertheless it is fully justified here.

Certainly there must be an element of selfishness, aside from stupidity, that holds up a consultation in these cases for months. One can quickly ascertain the value of a hospital's work by its list of consultations. The institution showing a large number of these is always the most efficient. Within the medical fraternity at large, amen, so be it. We believe this foreword is sufficient apology for our apparent harping on an old sore.

The cases about to appear before us are most interesting and instructive, but I have thought it might be well, even at the risk

of repetition, to discuss the underlying causes of this most important subject of urinary bleeding.

Before the advent of the modern school of urology (in the good old days of yore) we were wont to speak of hematuria as a distinct entity. Alas, even today one only too frequently hears the expression "essential hematuria." Essential hematuria, perish the thought! There can be no such thing. It is well,

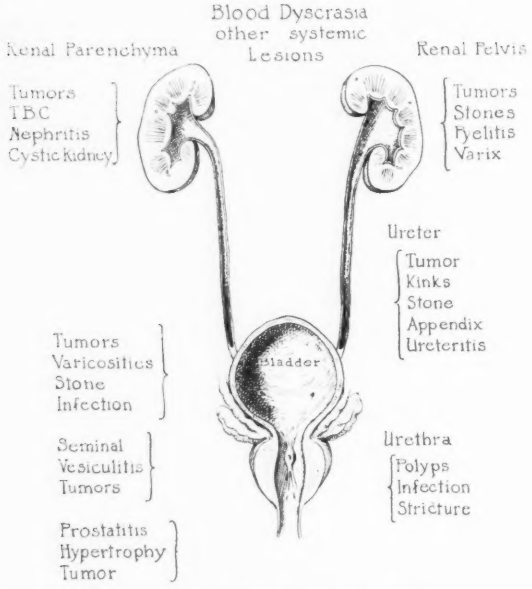

Fig. 140.—Sources of blood in the urine.

therefore, to relegate this expression, along with its close relatives, idiopathic and cryptogenic, to the archives of urologic history. Some years ago a well-known surgeon aptly said, "If one wishes to use the term 'essential hematuria' it should be done in the quietness of one's study, or among very intimate friends, but never in the presence of an intelligent patient." Remember, also, that it is not required of the patient to prove he is suffering from a grave condition, causing hematuria; rather is it the duty

of the physician to find out the source of bleeding, and to institute treatment as soon as possible.

Blood in the urine is a warning that calls for prompt investigation. This is a fact that may well be emphasized. In the era preceding scientific urology bloody urine was often treated by the application of ice-bags to the suprapubic, perineal, or renal regions. Hemostatic drugs were used rather liberally internally, and at times injected into the bladder via the urethra. If the lesion was of moment, the hemorrhage, when checked, usually returned. Alas, the cause of the bleeding was usually determined in the sanctum sanctorum of the pathologist.

The presence of blood in the urine, it is true, may be incidental to a minor lesion. Unfortunately, it registers only too often the presence of a grave pathologic entity, endangering the life of the patient. If the hematuria were only persistent and constant, it might awaken the physician from his lethargy. The bleeding, however, may be (in fact, only too often is) of such a transitory nature as to lull our colleagues into a false sense of security. Thus physicians may fail to arrive at a diagnosis until the patient has passed beyond surgical relief. After this there is nothing left but palliation and the services of another doctor, not of medicine, but of divinity.

Etiology.—What are the causes of hematuria? We believe that the etiologic factors may first be grouped into medicinal and surgical groups. See the tables herein prepared:

TABLE I

Medical Lesions

Diseases:

Other acute diseases:

Nephritis, acute.
Postdiphtheritic nephritis.
Oxaluria.

Acute febrile:

Malaria.
Scarlatina.
Typhoid.
Typhus.

Disease of the blood:

Anemia.
Hemophilia.
Leukemias.
Malaria.
Scurvy.

Poisoning and occupational diseases:

Arsenic.
Cantharides.
Phosphorus.
Turpentine.

Continued use of drugs:

Rhubarb.
Senna.
Sulphonal.
Trional.
Urotropin.

Parasites:

Schistosoma hæmatobium.
Filaria immitis.
Amœba urogenitalis.

TABLE II[1]

Surgical Causes

1. Trauma (general) of any part of the urinary system.
2. Traumas of childbirth.
3. Tumors of kidney:
   (*a*) Carcinoma.
   (*b*) Hypernephroma.
   (*c*) Papilloma of renal pelvis.
   (*d*) Sarcoma.
4. Other diseases of the kidney:
   (*a*) Pyelitis.
   (*b*) Stones.
   (*c*) Tuberculosis.
   (*d*) Varicosities
5. Diseases of the bladder:
   (*a*) Infection.
   (*b*) Stones.
   (*c*) Tumors.
   (*d*) Ulcers.
   (*e*) Varicosities.

[1] These charts do not represent all the causes of blood in the urine, but certainly those of greatest moment.

6. Diseases of the urethra:
   Male:
   (*a*) Infection.
   (*b*) Polypus or papilloma.
   Female:
   (*a*) Caruncle.
   (*b*) Tumor.
   (*c*) Urethritis.
   (*d*) Urethral prolapse.
7. Diseases of the prostate:
   (*a*) Prostatitis.
   (*b*) Adenoma.
   (*c*) Stone.
   (*d*) Carcinoma.
8. Diseases of the seminal vesicle:
   (*a*) Vesiculitis.
   (*b*) Tumors.
9. Urogenital tuberculosis.

You will now naturally say, You have given us most of the possible causes of blood in the urine, but we are interested in the common causes; what are they? The most common reasons for hematuria are those we have tabulated under surgical disease, and among these certainly stone, tumor, and tuberculosis are of paramount importance, and in the order named.

Elimination of Etiologic Factors.—How shall we proceed to eliminate the possible causes of hematuria? A carefully taken history is most essential and gives us a mine of information. The family history may throw much light on a family hemophilia, or the so-called "bleeder's disease." Other factors of importance may be elicited in regard to tuberculosis, tumors, or even purpuric conditions. In regard to purpura it is important to remember that we may not only have purpuric oozing, but that some students believe many bladder ulcers are primarily purpuric spots.

The previous personal history may recall a scarlet fever, a typhoid, typhus, malaria, a gonorrheal infection, or may suggest a postdiphtheritic nephritis. In this part of the history we may also inquire into any illness that may have led to the prolonged

use of drugs, as in nervous lesions, where hematuria is by no means rare. Neither can we overlook the popular use of cantharides as a sexual stimulant.

As to the age of the patient, we know that when he is past fifty years there is always a prostatic hypertrophy to be thought of, or a possible carcinoma of that gland.

As regards sex, we may think of, in the female, urethral caruncle, urethral prolapse, or possible accouchement injury. It is also of great import to rule out genital bleeding.

Occupation: Here we are faced by the question of occupational disease and the callings alluded to as dangerous trades. Workers in arsenic, phosphorus, turpentine (and some even accuse the alcohols) suffer not infrequently from attacks of hematuria. This is a common occurrence among painters, particularly when working in an ill-ventilated compartment.

In taking the present history we will carefully inquire into the possibility of any injury, recent or remote. If we do not do this, we may overlook an important factor, as in making our external examination it is easily missed. We have seen severe injuries of the internal organs without any visible external signs. Some four years ago we were called to see a man who had fallen from his bicycle while looping the loop. This man had marked hematuria, with a ruptured kidney necessitating nephrectomy, while externally there were no visible signs of injury in the renal area.

Character of the Bleeding.—In what manner does the bleeding occur, is it always present or is it intermittent? Does the bleeding precede the urination, that is, an initial hematuria? Is it intimately mixed with the urine? In considering an admixture we must not overlook the fact that we may have to deal with a hemoglobinuria and the color of the urine may not help us much. This is the condition which is common after the use of sulphonal or trional over long periods. Many times have we seen it in malaria. Here it is often referred to as black-water fever. A microscopic examination of the urine and that of the blood is of great assistance in eliminating malaria and the anemias as well.

Suppose blood-clots are found? It is important to know if they are fresh, of a dark red color, or do they look lighter and older? In some cases the hemorrhage is typical and we can at once recognize the source. For instance, one can be quite sure that bleeding which precedes the urine comes from the anterior urethra. This often occurs in severe urethritis, as in the so-called "Russiche-tripper" or the "hemorrhagica urethritis gonorrheica," as described by Glinger. It is true this bleeding may come from the deeper urethra. That, however, must be very rare, as it necessarily needs to be large in quantity. The associated symptoms would, indeed, quickly call our attention to the bladder.

Terminal bleeding causes one to think, first, in younger men of an acute posterior urethritis, which is surely its most common cause. This, you will remember, occurs at about the third week of the neisserian infection. Old inflammatory patches in the deep urethra have a habit of flaring up, at times many years after the original infection. It is, therefore, always well to keep in mind this old posterior urethritis. At times it will even cause an epididymitis. As the years go by and sixty is approached we begin to think of prostatic hypertrophy and carcinoma. Lesions of the vesicle neck, such as polyp or a small stone, aye, even a seminal vesiculitis, may cause the bleeding, the latter being, however, quite unusual.

Organic Bleeding.—When one attempts to accuse a particular organ he should determine if the bleeding is continuous or intermittent. We know that in such serious conditions as bladder bleeding the hemorrhage is often continuous or it may be checked by a clot. This may, also, be applied to the kidney. Do not forget that there are fallabilities in all our diagnostic procedures, as the cystoscope, Roentgen ray, etc. The greater number of diagnostic errors are in connection with kidney lesions.

In discussing vesical bleeding Thomas recently mentions no fewer than 66 causes, many, of course, being very rare. Lower, in a study of 2922 patients with urogenital disease, discovered hematuria in 798, or 26 per cent. He demonstrated conclusively that the true significance of hematuria as a diagnostic indication

lies not in the relationship of the primary cause of the total hematuria evidenced, but in the relationship of the occurrence of the bleeding to the primary cause. This is of great importance.

Thomas, in 632 patients with many symptoms, found 430, or 68 per cent., with hematuria. In 216, or 50.2 per cent., the bleeding was of vesical origin. In 33.7 per cent. it was of ureteral or renal origin, and in 4.2 per cent. it was impossible to distinguish between these two respectively. In 18.3 per cent. the blood was of prostatic, spermatocystic, or urethral origin. In 2.5 per cent. its source could not be determined. Certainly we may all envy Thomas this wonderful record.

In MacKenzie's series of 821 cases with hematuria 52.7 per cent. were from the upper urinary tract, and 47.3 per cent. from the lower.

In MacKenzie's series of 100 cases 28 were of renal origin, and in one-half of the cases the bleeding was caused by bladder tumors. In discussing renal lesions Herman states that simple inflammation, calculus formation, and tuberculosis account for more than twice as many renal hematurias as all other lesions, including tumors. The latter states that one of three renal hematurias is caused by a tumor.

We know that while blood is frequent in renal tumors, it often does not appear until the tumor is beyond help surgically. We believe there is but one really typical feature of renal disease; that is, where we have a sudden profuse bleeding from the kidney, it is usually of neoplastic origin.

In many of the serious lesions bleeding may be either intermittent or continuous, as in tumor, tuberculosis, and stones of the kidney. As we said a little while ago, the bleeding of renal tumor while most often intermittent is of marked intensity. I would like you also to remember that small tumors may produce as much bleeding as the larger masses. Therefore the amount of oozing is not of so much importance as the mere presence of hematuria.

Unfortunately most mistakes are made in the intermittent hemorrhage. Yes, sir, that is where we procrastinate. The

physician usually gives a little medicine and waits to see what will happen. His patient waiting is often rewarded by having the tuberculosis, at first limited to one kidney, become a bilateral infection. Our supposed benign tumor becomes a malignant one, with a thrombosis of the renal vein.

Examination of the Patient.—Following the carefully taken history, we proceed to digest the facts obtained, and are then ready for our physical examination. If the services of competent internists are available, they should always be called in to assist us in these cases. At the risk of repetition, we say again there is no other group in which co-operation is so essential as in the hematurias. Do not refuse to admit that someone else is a better chest man than you. Your consolation will come when he asks you to see his case. Selfishness does us no good, and only adds to the toil of the weary embalmer.

Do not limit yourself to the organ or group that you suspect. Let your survey cover the entire body. The general appearance of the patient is often a tell-tale. The eyes, the lips, the buccal mucosa, and the throat have verily a little message written on their surfaces, visible to the keen observer. The glands of the neck, the supraclavicular spaces must not be missed. The heart, lungs, and mediastinum often lead us toward tuberculosis, tumor, or a morbis cordis valvulorem—by no means rare factors in the production of bloody urine. The careful application of physical diagnostic methods to the abdomen must be considered. In this connection remember the diagnostic methods of J. B. Murphy in percussing the biliary and nephritic areas. Fist pounding over the kidney is almost diagnostic of renal retention when it causes pain.

In approaching the genitalia, of course look for a urethral discharge. Only recently we were treating an elderly man in the dispensary for a gonorrhea. A posterior urethritis with bleeding and a prostatic abscess appeared. During the night he developed a urinary obstruction and was removed to a hospital. There, in view of his age and the bleeding, together with an enlarged prostate, a diagnosis of hypertrophy of that gland was made and an immediate prostatectomy attempted. Suffice to

say he was saved with difficulty. In the examination his penis and urethra were never thought of.

At times we will note a swelling in the perineum. This with a history of trauma suggests a urethral injury, possibly a rupture. In the absence of injury we naturally think of stricture with extravasation of urine, or a pus perineum. Let me impress on you a very important point, *i. e.*, regard all tumors of the perineum in the male with suspicion. With the presence of blood the diagnosis is certain. Here we are usually called on for an immediate external urethrotomy.

Tumors may be visible or palpable in the suprapubic area. A palpable suprapubic mass often means an involvement of the bladder dome. We recently saw a case in this clinic where we were unable to cystoscope. A provisional diagnosis of bladder-dome tumor was made and exploration advised. As he was an elderly man, another surgeon decided to remove the prostate. After this unnecessary procedure, the bladder tumor was found.

Rectal palpation, though regarded by some as an indelicate procedure, is one of the most useful diagnostic measures. It gives the urologist a vast amount of information regarding the prostate, vesicles, and lower urinary tract. It is of equal value in other tracts.

Vaginal examination in the female leads us not only to urethral and vesical disease, but at times to the ureter. After some experience, palpation of the ureters by the method of A. M. Judd will elicit much valuable information. This is particularly true in ureteral stone and tuberculosis. We have demonstrated this frequently in the former, and in the latter the feel of the ureter is diagnostic.

The Complete Urologic Examination.—By the simple means previously described we have eliminated the urethra as a source of the bleeding. We are now coming into our own with the examination of the urinary tract above the vesical sphincter. It has seemed to us that as there is a patron saint for most everything these days, the medical man is entitled to a few representatives in this field. These facts being conceded we should

certainly canonize Max Nitze, Albarran, and Roentgen. This is but a mild tribute to distinguished memories.

We like to place ourselves in the patient's position and, having had a personal experience with the cystoscope, advise the employment of local anesthesia. On numerous occasions our attempts to anesthetize the urethra by instillation of novocain have been ridiculed. I can assure you, gentlemen, that our critics are in error, as surface novocain does reduce the sensibility of the parts considerably. In many the anesthesia is complete.

The cysto-urethroscope, particularly of the Goldschmidt type, gives us a good view of the deep urethra and bladder. Tumors or other lesions are quickly seen and noted. When we pass into the bladder with our instrument, we must be prepared to irrigate. This is the point where the American instrument is superior. European makers have at last been compelled to recognize this principle. Should we find blood in the bladder and we are able to remove it in a reasonable time by irrigation, we can be quite sure that the bleeding is in the urinary tract above the bladder. If removed with difficulty the hemorrhage is most likely in the bladder.

What shall we expect to find as a most likely cause of bleeding in the bladder? Chiefly foreign bodies—ulcers, tuberculosis, neoplasms, and at times varices. If we find purpuric spots, it will suggest ulcer, or a purpuric bladder lesion. Most ulcers are tubercular or should be considered so until proved otherwise. At this point let me call your attention to the fact that tubercles are present in the bladder in not over 20 per cent. of patients with tuberculosis of that organ. It was long held that tubercular ulcers near a ureteral orifice meant tuberculosis of the corresponding kidney. Rovsing demonstrated that this was not an actuality, the reverse often being true, that is, the tuberculosis was in the opposite kidney.

Should we find bleeding from one or both orifices, we are justified in passing a catheter up into the pelvis of the kidney and examining the collected urine, at the same time carrying out our functional tests. Roentgen technic will also aid us greatly in an examination as, when combined with the ureteral

catheter, it quickly rules out ureteral disease. Humer believes that stricture of the ureter plays a very important part in urinary bleeding, the so-called "obscure types."

The principal diseases left to consider are those of the kidney and its pelvis. Tumor, stones, and tuberculosis are the lesions causing most bleeding. Eisendrath says that hematuria occurs as an initial symptom of tumor of the kidney in 30 to 60 per cent. of the cases, according to statistics. It occurs as an associated symptom, that is, with pain, tumor, etc., in an average of 78 to 80 per cent. of the cases. There is a great variation in the duration and the extent of the hematuria, and the same is true of its tendency to recurrence. The urine in a renal tumor patient contains more blood than in any other condition except papilloma of the bladder. The demonstration of a tumor, the pain over it, and the hematuria make the diagnosis certain. To be of real use the diagnosis must, however, come a little earlier than this.

Kretchmer states hematuria is more common in tumors of the bladder than in renal growths. In a series of 238 cases he found 60 per cent. due to bladder neoplasms, about equally divided between benign and malignant; 14 per cent. due to kidney tumors. Cabot in 344 cases found 24 per cent. incident to bladder tumor and 12 per cent. to new growths in the kidney.

In tuberculosis of the kidney the bleeding from the ureter, demonstration of the tubercle bacillus, and the pain over the renal area are, as a rule, quite conclusive. At times the bacilli are scarce and may be detected by the method of Crabtree. If that fails, guinea-pig inoculations may be used. One hears from time to time quite a little of the Bloch methods. These procedures are supposed to hurry the development of the tubercle bacilli in the pig by exposing it to the *x*-ray or by injuring the inguinal glands. My friends of long experience do not regard these methods with much favor. In the closed types of renal tuberculosis we find no bacilli in the urine. We must, therefore, depend on other local signs and the use of the Roentgen ray. Tuberculosis of the kidney usually presents itself as quite a typical picture on the film.

In renal calculus we usually have the history of the typical

crises, which are very severe. In fact, they can only be appreciated by one who has gone through them. The pain may start in the lumbar region and extend as far as the tip of the penis. The *x*-ray is our real friend in kidney stone. We can be sure of a shadow in at least 80 per cent. of these cases. Uric acid stones are often overlooked, but usually found after several attempts. In connection with kidney pictures, let me tell you it is just as important to take them from several angles as it is fractures.

In order to bring out dimly appearing or uric acid stones Kummel of Hamburg injected a rather thick solution of collargol into the kidney pelvis, and left it overnight. Kummel states that stones treated in this way showed quite clearly on the plate. Stones that produce bleeding are practically always in the renal pelvis and produce, as a rule, varying degrees of functional interference. This we can demonstrate by the use of phenolsulphonephthalein, which you all know. Not all kidney stones produce pain, but the majority do. The calculus is not at all unusual.

In connection with bleeding from the urinary tract Corbus tells us that a great amount of speculation has been brought forward in regard to the etiologic factors in so-called "essential hematuria." Few, however, have considered the possibilities of secondary ulcer to gummatous formation. Therefore, it might be well to eliminate syphilitic infection before ascribing the case to some doubtful etiology. These remarks, while by no means fully covering this important subject, we are sure will aid us in our search for the light.

As a further aid we present the histories of a few interesting cases presenting bloody urine as a diagnostic problem.

Bladder Case.—J. E. Z., male, white, aged sixty-three.

Chief Complaint.—Hematuria and frequency of urination.

Family History.—Mother died at seventy of pneumonia; father at seventy-four, apparently of apoplexy. One sister died at about thirty-five of some lesion associated with the post-partum period, probably sepsis. One brother died at thirty of influenza. Two sisters living and well.

Previous General History.—Thinks he had scarlatina and measles in childhood. Numerous attacks of tonsillitis between

twenty and forty, none since. Appendectomy at twenty-seven. He has had several attacks of what was called musculospiral neuritis. Our patient feels that none of the aforementioned was serious, and he has generally been in good health.

Previous Urologic History.—Denies any venereal infection or urologic lesion.

Present Illness.—Three years ago, patient states, on several occasions he noticed the urine was slightly reddish in color. This, however, quickly disappeared. About six months later he became aware of the fact that the red coloration had again appeared

Fig. 141.—Varicose veins of bladder.

and tended to persist. He went to his local physician, who told him it would soon clear up, and there was no cause for worry. The bleeding did not subside entirely, but became intermittent and so continued. About eighteen months ago he noticed a gradual increase in frequency of urination. The urine now was red most of the time and a terminal bleeding made its appearance. The hopeful physician now tried a new treatment and the urine cleared once more. This process was repeated several times. He then began to pass clots in the urine and at times the stream would stop entirely.

When we first saw the patient he seemed rather weak and flabby, appearing much older than his actual years. The color of his skin is now a greenish-yellow hue. His appetite is good; owing to nocturia he does not sleep well. A very strong urinous odor surrounds the patient, and on removing his clothing the underwear is markedly stained with bloody urine. A drop of blood is also noticed at the meatus.

Physical Examination.—Heart and lungs showed no apparent abnormalities. Abdominal examination shows marked tympanitis above the umbilicus. Suprapubic area suggests a tendency to dulness, mostly in the midline. Palpation suggests an indefinite mass just above the symphysis. Rectal examination shows a slightly enlarged prostate. Seminal vesicles are not palpable. We note that patient passes a little urine every few minutes. It is bloody and then followed by pure blood.

The urine is acid, 1.030, contains considerable albumin and a few hyaline casts. The microscopic examination shows red blood-cells in vast amounts.

Blood Examination.—Red blood-cells 3,969,000, whites 7250, hemoglobin 60 per cent., polymorphonuclears 65 per cent., lymphocytes 30 per cent., mononuclears 4.5 per cent., eosinophils $\frac{1}{2}$ per cent. Blood-chemistry reveals a slight increase in nitrogen retention.

Cystoscopy.—This examination was first refused, but two days later consented to. The bladder was found filled with such a large mass of blood-clots that it was at first impossible to see anything. The clots were finally removed by the method suggested by Cochrane. A Chismore evacuator was introduced and peroxid of hydrogen forced through it. In a short time many of the clots were pretty well dissolved and drawn out through the evacuator.

The bladder was then filled with sterile boric acid and a cystoscope reintroduced. The solution was soon discolored, but sufficient time was given to note that aside from a moderate prostatic enlargement there were no evidences of bladder growth. The ureters appeared very small and retracted. Slightly above the interureteral bar in the midline we note a rosette-like group

of varicosities. The bleeding seemed to come from this mass, and after a little difficulty the exact part was located. Ligation of the mass controlled the hemorrhage.

Kidney Case.—Mrs. J. G., white, aged fifty-two, native of Poland. Seen in consultation with Dr. M. F. Goldberger.

Present Complaint.—Hematuria and backache.

Family History.—One brother known to have died of pneumonia at twenty-four years. Unfamiliar with the remainder of her family story.

Fig. 142.—Pyelogram of kidney case.

Previous Personal History.—Thinks she had variola in infancy and several attacks of tonsillitis in her early youth. When she reached the age of thirty began having attacks of rheumatism. This condition she believes during the past two years has settled in her back. The family physican, it is said, called it lumbago.

Previous Urologic History.—Denies any venereal or urologic manifestations.

Present Illness.—About six months ago she noticed that her

urine was red and that it contained blood-clots. She also became aware of the fact that her lumbago was worse, particularly so on the left side. Her physician found it necessary to administer morphin for relief of the pain. In a few days the blood disappeared from the urine and the doctor's services were dispensed

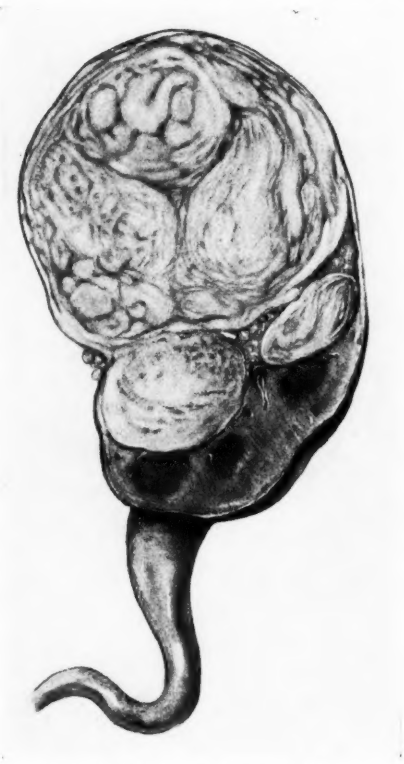

Fig. 143.—Adenocarcinoma of kidney.

with. The pain over the left renal area still persisted, but was somewhat mitigated by the use of various plasters and greases. Two months later the bleeding recurred, but soon ceased. About three weeks before we saw the patient bleeding again appeared and has since been continuous. The lumbago or pain in the

left renal area is worse. When she was referred to us for a complete urologic examination we noted the following:

Patient is a rather well-built woman of fifty-two who complains of renal pain or "lumbago" as she calls it. You will note particularly that this has been in evidence for two years. Do not overlook these persistent back pains. They are often masking a very serious malady. She seems much amazed because no doctor is able to stop the blood or relieve her back pain without morphin. This latter is significant. Dr. John B. Deaver used to tell us that in these severe pains it was not morphin that was needed, but the antiphlogistic touch of the therapeutic knife.

Physical examination of the chest and abdomen, including pelvic organs, was made by competent examiners and reported negative.

Percussion over the left kidney elicits marked pain. Not so on the right side. No mass is palpable anywhere. On rectal examination she is sensitive, but this is probably incident to the presence of a hemorrhoidal mass.

Her blood examination reveals a red count of 3,960,000 and hemoglobin of 80 per cent. Blood-chemistry suggests a slight nitrogen retention. Wassermann negative.

Urine.—Acid 1.024, slight trace of albumin, loaded with red cells, a few white cells and some granular and hyaline casts.

Cystoscopy.—Instrument passes readily: vesical neck and bladder appear to be normal. Urine from the right ureteral orifice is bloody. Both openings of ureters are normal and catheters pass readily to both renal pelves.

Examination of kidney urine is as follows:

	Right.	*Left.*
Urea	Trace	1½ per cent.
Microscopic	Loaded R. B. C.	Epithelial cells
Tubercle bacilli	Negative	Negative
Culture	Staphylococcus albus	Negative
Phthalein	Appears as slight trace in twenty minutes	Four minutes in appearing

Pyelogram and ureterogram show an almost complete kidney filling defect (Fig. 142). There is a small area of the pelvis left.

It suggests a cup-like pouch in which something may be sitting. This means we have a large tumor mass replacing almost all of the kidney substance except an area near the lower pole. Truly a mass is sitting in one cup. You will notice, also, that the kidney is displaced downward toward the crest of the pelvis.

Fig. 144.—Cystogram of seminal vesicle tumor.

The infected ureter here stands out beautifully, showing a distinct loop. This picture well shows the value of ureterography. In Fig. 143 you see how well the specimen fits in with our diagnostic procedure. A nephrectomy in this case confirmed our diagnosis of adenocarcinoma of the kidney.

Vesicle Case.—G. L., white, aged forty-nine, married. Father of five children.

Chief Complaint.—Blood in urine and pain over bladder.

Family History.—Mother and father said to have died of senility. No other history obtainable.

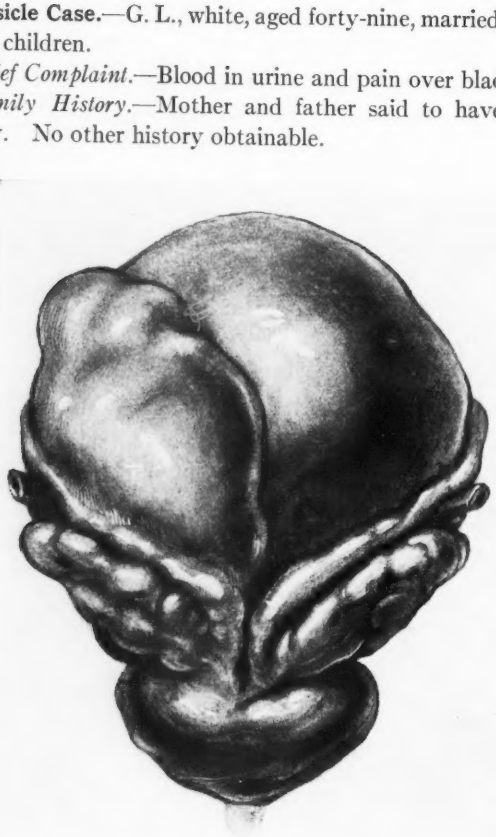

Fig. 145.—Carcinoma of left seminal vesicle.

Previous Personal History.—Aside from an attack of tonsillitis believes he has always been well.

Present Illness.—About one year ago he noticed a urethral discharge. It was called a strain by several physicians, as gonococci were found in it. In spite of treatment to the urethra the discharge persisted and about six months later became bloody. Patient also noticed that he was losing sexual desires. In spite

of this nightly emissions occurred about once a week and were quite bloody. Two months ago noted that there was always blood in the urine, and about the same time noticed he was losing in weight and strength. He has been to a number of specialists, has been cysto-urethroscoped and diagnosed as chronic urethritis. Several of the physicians have made rectal examinations, all reporting the prostate normal. Please remember that a rectal examination does not stop at the prostate, but must include the vesicles at times well above the prostate. Also remember that it cannot be done with a quick swing of the fingers. When you examine a prostate push your finger up in the median raphé to its upper border, follow this out along the cornices to the wing of the prostate. Extending up from the latter you will usually find the vesicles. To continue with our history. Examination on admission showed an exhausted man with a bloody urethral discharge and hematuria. Rectal examination reveals an apparently normal prostate. However, above and to the left of the prostate there is a large mass corresponding to the site of the seminal vesicle. This mass is distinctly irregular and lumpy. We are unable to feel its upper pole.

Cystoscopic examination shows us a marked bulging of the left posterior bladder wall with much congestion. This area suggests a tumor, but it is very difficult to tell if it is outside or inside the bladder. On withdrawing our instrument into the area of the verumontanum we noticed blood extending from the left ejaculatory duct. A cystogram suggests a diverticulum of considerable size or a division of the bladder into two parts; this because of the fact that the injection on the left appears distinctly separated from that on the right; a diagnosis of tumor of seminal vesicle was made. Surgery was unavailing and the presence of a carcinoma of the vesicles was discovered at autopsy.

CLINIC OF DR. MAXIMILIAN A. RAMIREZ

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DISEASE OF THE UPPER RESPIRATORY TRACT IN BRONCHIAL ASTHMA

CONTINUED investigation into the causation of bronchial asthma seems to indicate that a multiplicity of factors may contribute toward the production of this condition. In some instances but a single etiologic basis appears to be present; in others the make-up is more complex. Determination of the underlying cause in the particular case under consideration becomes an individual problem.

Rackemann[1] has divided asthmatics into two groups: those sensitive to foreign proteins in which the cause is outside the body (extrinsic); and those not sensitive, the cause being located within the human organism (intrinsic). The latter group comprised 53 per cent. of Rackemann's cases,[2] 28 per cent. being of the extrinsic type; in 19 per cent. the causative factor was undetermined. This classification seems a logical one to employ as a working basis. It must, however, be apparent that asthmatic individuals frequently come within both of these groups.

Through the employment of dermal tests hypersensitiveness to a specific foreign protein may be determined and immunity to the offending substance or substances be established.

It is recognized that bacteria play an important rôle in the etiology of intrinsic asthmas. The focus may be in the intestinal tract, the teeth, the lungs, tonsils, the nose, nasopharynx, or sinuses, etc.

The purpose of this report is to indicate the frequency of infection in the upper respiratory tract, and to emphasize the

importance of its thorough elimination in bronchial asthma. McGinnis,[3] Clarke,[4] Bishop,[5] Lintz,[6] and Stout[7] in recent reports have indicated the importance of this particular phase of the problem. In my own work I have found infection in the nasal cavity and accessory sinuses to be a most important contributory factor in atopic cases in which the paroxysm is primarily due to hypersensitiveness to a specific protein, and in the non-atopic group it is frequently the sole etiologic factor.

The value of skin reactions to bacterial extracts or emulsions, in the diagnosis of allergic relationship, is a much disputed question.

Brown,[8] employing the intradermal method with autogenous vaccines prepared from the nasal secretions and sputum, holds that while little diagnostic information is to be derived from immediate reactions, those interpreted within twenty-four hours are fairly reliable. Thomas, Famulener, and Touart[9] also express a preference for the intradermal procedure in determining bacterial hypersensitiveness. Secretions from the nose, ethmoids, and antra were used in their series of 134 cases. They noted two types of positive reaction: an early one, appearing within one-half hour and fading soon thereafter; also a late reaction observed within twelve hours, usually persisting for from two to five days.

These authors rely a good deal on skin tests as an indication of bacterial allergy.

Cooke[10] observed no immediate allergic reactions from bacterial preparations in any of his cases. The mere increase in the degree of an existing asthma twelve to twenty-four hours after injection, he concludes, is not sufficient evidence to be regarded as proof. McLaughlin[11] likewise attributes little significance to a positive reaction, believing it to be merely an indication that the skin is oversensitive. Conversely, no reaction is seen oftentimes in instances where dark sinuses, etc., are shown by transillumination or *x*-ray. This occurred in about 30 per cent. of Stout's series.[7] It is my personal impression that the specificity of both the dermal and the intradermal tests with bacterial emulsions remains unproved. I have found them variable and unreliable.

In many cases the formation of polypi or the presence of a deviated septum undoubtedly predisposes to infection in the nose, nasopharynx, or the accessory sinuses. Admitting, then, that infection may exist as a primary or secondary etiologic factor in some cases of bronchial asthma, its removal is a logical procedure. Included among the various therapeutic measures employed are irrigation, topical applications of antiseptics, ultraviolet radiation, antrum puncture, removal of nasal polypi, correction of deformities, etc.

The following cases, selected from a large series, are herewith presented merely to emphasize the importance of locating and properly treating disease in the upper respiratory tract in all cases of bronchial asthma.

Case I.—Female, aged thirty-one years. Patient gave a history of frequent attacks of asthma since the age of five. Has had asthma almost constantly for past year; occasional sneezing; frequent headaches; menstrual history normal; intestinal action normal. Skin tests showed a strongly positive reaction to horse dandruff. Transillumination and *x*-ray demonstrated an exudate in the right antrum. Inoculations with horse dandruff were started and right antrum punctured and irrigated. Symptoms improved immediately, but returned several weeks later. Antrum continued refilling, and after two or three months' treatment—although patient was fairly well immunized against horse dandruff—the symptoms still continued. A large puncture was then made in right antrum by Dr. John McCoy. Antrum thoroughly drained and kept free of exudate. Patient has now been free of asthma for more than a year, having received no treatment for about four months.

Case II.—Female, aged twenty-seven years. Asthma, on and off, for past two years. Considerable sneezing summer and winter. Positive reaction to orris root and goose feathers demonstrated by means of skin tests. Transillumination and *x*-ray showed an exudate in both antra. Immunization against orris root and goose feathers was instituted and contact with orris

root and goose feathers eliminated as much as possible. Symptoms continued until both antra were thoroughly drained and kept free of exudate, after which the patient remained free of asthma. In January of this year patient was still symptom free—eight months after her last treatment.

Case III.—Female, aged twenty-five years. Asthma at various times for four years. Considerable sneezing and nasal discharge in winter. Skin tests were all negative. Examination of nose showed polypi, both sides. Transillumination and *x*-ray of sinuses negative. Symptoms disappeared completely after removal of polypi. Four months later patient returned with recurrence of dyspnea, and examination showed return of polypi on right side. Removal of two large polypi was followed by immediate disappearance of the symptoms, which have not returned up to the present time—four months after last attack.

Case IV.—Male, aged fourteen years. Repeated attacks of asthma for past two years. Frequent head colds summer and winter. Skin tests with foods, epidermals, and pollens all negative Examination showed marked hypertrophy of the turbinates on both sides and considerable mucopurulent secretion in nose and nasopharynx. Transillumination and *x*-ray of sinuses negative. Patient given a daily saline irrigation of nose, followed by neosolvol spray, argyrol pack once a week, and intranasal ultraviolet treatments with Kromayer lamp. Attacks of asthma gradually diminished and finally disappeared coincident with improvement in the nasal condition. This patient has now been free of asthma for more than nine months.

Case V.—Male, aged thirty-five years. Asthma for past six years. No hay-fever, no headaches, sneezing, nasal discharge or any other symptoms referable to the nose and accessory sinuses. Family history negative for allergy. Skin tests of a variety of foods, epidermals, and pollens were all negative. Examination of nose showed numerous polypi on right side. Transillumination and *x*-ray of sinuses demonstrated the presence of an exudate in

right frontal sinus. All sorts of treatments were given without avail. The asthma was finally completely relieved by a radical frontal sinus operation performed by Dr. John McCoy. This patient has now been free of symptoms for about eight months.

CONCLUSIONS

1. Disease in the nose, nasopharynx, or accessory sinuses is a frequent finding in bronchial asthma. It may be a contributory factor in atopic cases in which the paroxysm is primarily due to hypersensitiveness to a specific protein. In persistent cases of the non-atopic type it may be the sole cause.

2. Bacterial skin tests, in the diagnosis of allergic relationship, have proved uncertain and unreliable in my experience.

3. Infection in the upper respiratory tract must be thoroughly eliminated, whether the condition is caused by a specific allergen or whether it is non-allergic in nature.

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CLINIC OF DR. HORACE S. BALDWIN

ASTHMA CLINIC, CORNELL UNIVERSITY MEDICAL COLLEGE

CLINICAL ASPECTS OF CHRONIC BRONCHIAL ASTHMA

THE remarkable advances in the field of allergy and its clinical application have tended greatly to clarify the hitherto confused picture of bronchial asthma and to facilitate the treatment of this condition. With the development in our knowledge of the relation of allergy to asthma there has been a danger of minimizing the factors of infection, non-specific excitants of the asthmatic paroxysm, the relation of the nose and accessory sinuses, and the important constitutional changes that occur in the organism either dependent upon or independent of the asthmatic state.

The Asthma Department at the Cornell Clinic is a subhead of the Department of Internal Medicine. In addition to the special examination into the allergic history and the tests for allergy every patient is studied as a problem in internal medicine; the history taking includes a review of the various systems and the physical examination includes the routine physical examination of the internist as well as the more specially adapted one for the asthmatic. This latter embraces thorough examination of the nose and accessory sinuses, and various measurements of the chest. A vital capacity determination is made on every patient, his condition noted at the time of the determination, and this is repeated during the course of treatment at varying intervals. This test has been very interesting and helpful in evaluating the amount of impairment of respiratory ventilation and serves often as an index of improvement. The physical examination form is especially designed to estimate the amount of organic change

in the lungs and thorax and when repeated at intervals serves as a guide to progress.

The chronic bronchial asthmatic so often develops trouble in the nose and accessory sinuses that it is important to have the nose carefully examined. The detection and treatment of chronic sinus disease is of the utmost importance, especially when it involves the maxillary antra and ethmoid cells. The removal of polypi when present will often result in marked improvement. Occasionally a submucous resection may be indicated, although in our clinic we have not been impressed with the results from this measure. Many chronic bronchial asthmatics have very irritable mucous membranes, and irritation of these causes reflex stimulation of the vagus as described by Brody and Dixon a number of years ago, with resultant bronchial spasm. Local treatment designed to reduce the irritation and congestion of these membranes is often helpful. Of course, the removal of infected tonsils is indicated, a measure that reduces the tendency to recurrent bronchial infections and the resultant irritation and hyperexcitability of the bronchial mucous membranes. In short, even though the question of asthma as a result of direct allergy to infection is still unsettled, there is no doubt that infection in the respiratory tract, including the accessory sinuses, causes a lowering of the threshold to the various excitants of bronchial spasm. Where infection is present it should be eliminated, and if there are polypi and spurs or a chronically inflamed nasal mucous membrane these must be treated with the purpose of developing a tissue that is not so irritable.

The determination of organic disease in the lungs and heart is of great value in prognosis and in furnishing to the physician a background for therapy. If a patient has chronic emphysema together with his bronchial spasm, the dyspnea dependent upon the emphysema must be accepted as representing the results of an organic and constitutional change which does not yield readily to therapy. Fortunately for the asthmatic it seems to take considerable asthma over a long period of time to develop a chronic emphysema which does not disappear with the relief of bronchial spasm. Bronchiectasis is a heavy handicap in the

asthmatic. At the Cornell Clinic, with the help of Dr. Arthur Palmer of the Nose and Throat Department and Dr. John R. Carty of the *x*-Ray Department, we have been making a study of the development of bronchiectasis in the chronic asthmatic by means of lipiodol injections of the bronchial tree. The result has been to show that comparatively few cases of even long-standing asthma develop bronchiectasis. Where present, the results of treatment of the asthmatic state have been most discouraging.

It is not unusual to find cardiac weakness in the subject of chronic bronchial asthma. Where the cardiac condition is treated improvement in the bronchial spasm usually results. The most frequent cardiac complications that we have encountered have been hypertension and auricular fibrillation.

Below is reproduced a history form which has been found useful in the clinic and private practice.

CLINIC OF THE CORNELL UNIVERSITY MEDICAL COLLEGE

Date Name
No. A.
Dept.

Chief complaint:
Onset: First attack—Year and date:
Preceding infections, allergic contacts, and symptoms.
Character of attacks:
Frequency and seasonal influence:
Occupation and bearing on asthma:
Nose and throat history:
Pulmonary infections:
Allergic inhalants in environment (pets, stables, factories, cosmetics, bedding, insecticides, miscellaneous):
Food allergy:
Dust history:
Non-specific excitants (temperature, humidity, emotional, digestive, exertion, irritants):
Skin lesions:
Family history:
Previous therapy:
Systemic review:

As will be seen, emphasis is placed on the features found in connection with the first attack. It is distinctly helpful to know

whether the attack started during the pollen season or in the winter, whether it occurred after a respiratory infection, sinusitis, operative interference with the nose, or following some change in the environment accompanied by the introduction of some allergic inhalant, etc. Occupation has considerable bearing. Tobacco trades, trucking, the dusty trades, various chemical industries, and many other occupations will often furnish the clue for either the cause or contributory factors. A history of the relation of foods to the attack is very important particularly in children. The dust history is assuming more and greater weight in the treatment of asthma. Housewives are particularly prone to this form of sensitivity, and treatments with autogenous dust extracts together with measures to eliminate dust or the wearing of dust masks are oftentimes very successful. We have been greatly interested in the non-specific excitants to bronchial spasm. A comprehensive idea of the various physical and other factors which cause bronchial spasm is of great importance in treating the individual case of chronic bronchial asthma. The patient can often be taught a mode of life that eliminates and minimizes these excitants, with the result that the severity of the bronchial spasm is greatly minimized. Last but not least important is the systemic review which may disclose serious constitutional disease accompanying the asthmatic state.

Date Name
No.
Dept. Asthma

Vital capacity Ht. Wt. S. A. Av. weight
Max. c.c. in 3 to 5 attempts.
Percentage normal.
Condition today:

Habitus Hypersthenic Sthenic Hyposthenic Asthenic

Chest: Shape: Louis' angle Kyphosis
Movement: Hoover's sign
Palpation:
Resonance: General.
Liver dulness anteriorly.
Lung resonance posteriorly.
Increase after inspiration.
Breath sounds:
Râles:

Measurements:	A. P. diameter.	Thoracic index.
	Lateral diameter.	
	Circumference.	Expansion.
	Subcostal angle.	
General:	Heart.	
	Arteries.	
	Blood-pressure.	
	Abdomen.	
Miscellaneous:		

The form of physical examination is not meant to supplant the thorough routine physical examination, but to add to it certain features which tend to present a definite picture of lung ventilation and organic change in the lung and thorax which may have occurred. A note is made as to whether the patient is asthmatic at the time of the examination. Vital capacity is then determined. In the absence of cardiac disease, and bronchial spasm at the time of examination, a low vital capacity usually means chronic emphysema with definite impairment of lung ventilation, and has considerable significance in limiting the prognosis and the problem of treatment. The habitus together with the presence or absence of over-prominence of Louis' angle and dorsal kyphosis, the movement of the chest—whether en masse or the normal expansion—the presence of Hoover's sign are noted. The location of liver dulness anteriorly and the lower limit of the lung resonance posteriorly give an idea as to the expansiveness of the lung. It is not unusual to find an asthmatic with only mild symptoms showing no definite liver dulness anteriorly as low as the eighth intercostal space and to find lung resonance posteriorly below the angle of the scapula as low as the first lumbar spine. When emphysema has occurred the lower limits of lung resonance are increased the increase in resonance at the lower limits on inspiration is very little or absent, and these findings are present in the absence of bronchial spasm on repeated examinations. Measurements of the anterior-posterior diameter, lateral diameter, circumference, and expansion of the chest and the extent of the subcostal angle are interesting and give an idea of the changes that have taken place in the bony thorax.

At the Cornell Clinic the skin testing is done by means of the

intradermal method, using protein extracts prepared by Dr. A. L. Coca of the Department of Immunology of Cornell University and The New York Hospital. We are using more and more for the children the method of passive transfer described by Walzer. This is a very simple procedure and the results are reliable. Its great advantage lies in the fact that small children are saved any possibility of a general reaction occurring from the intradermal infection and one does not have to combat the antics of a fearful and obstinate child who objects to the testing. In short, this measure consists of the withdrawal of 5 to 10 c.c. of blood from the patient. It is defibrinated, the serum taken off under sterile precautions, and a number of injections of 1 20 to 1 10 c.c. made into the skin of the relative. After forty-eight hours these sites can be tested by injecting the protein solutions. The same skin reactions occur as are found in the child. Control tests are made in unsensitized sites. The skin passively sensitized maintains its reactivity for about four weeks.

We have divided our extracts into two series, the first representing the inhalants and the second the common foods. Tests with vegetables, fruits, fish, and miscellaneous proteins are done when indicated. Very seldom is it necessary to test out against more than 50 proteins. The history, a careful analysis of the environment, and dietary offer more important evidence than the wholesale testing of a multitude of irrelevant proteins.

CLINIC OF THE CORNELL UNIVERSITY MEDICAL COLLEGE
DEPARTMENT OF ASTHMA AND HAY-FEVER

Name History No.

Skin Test Reactions

Series I.		Vegetables.	Fish.
Plantain	Goat epithelium	White potato	Salmon
Timothy	Mixed feathers	Sweet potato	White fish
Ragweed	Tobacco	Spinach	Cod fish
Orris root	Pyrethrum	Cabbage	Crab
Stock dust	Cotton seed	Lima beans	Shrimp
Horse epithelium	Sheep's wool	Peas	Oyster
Cat epithelium	Wheat	Carrots	Halibut
Dog epithelium	Rice	Tomatoes	Herring
Rabbit epithelium		Asparagus	Lobster
		Lettuce	

	Series II.	Fruits.	Own dust.
Wheat	Beef	Grapefruit	Miscellaneous
Corn	Lamb	Strawberry	
Rice	Pork	Raspberry	
Rye	Chocolate	Grape	
Oats	Peanut	Peach	
Buckwheat	Almond	Plum	
Whole milk	Cocoanut	Apple	
Egg	Mustard	Prunes	
Chicken	Black pepper	Orange	
		Lemon	

Sometimes an extract of dust from the patient's home or business environment will give a markedly positive reaction. In these cases in the absence of a positive reaction with the ordinary single inhalants it is necessary to make a detailed survey of the possible factors present and find which component of the dust is responsible. Occasionally this is impossible and then it is necessary to use the extract for desensitizing purposes.

In conclusion, the purpose of this clinic has been to emphasize the many sided aspects of the asthma problem. Thoroughness of history taking is necessary in order to grasp the problem of the individual patient. A determination of the amount of constitutional damage already present is essential in order that treatment may be intelligently handled. Finally the problem is intimately related to the field of allergy and infection. When the bronchial asthmatic is studied thoroughly along these lines treatment in a very large proportion of cases is helpful.

CLINIC OF DRS. MARCUS RAYNER CARO AND TIMOTHY J. RIORDAN

FROM THE DEPARTMENT OF DERMATOLOGY AND SYPHILOLOGY, UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE, SERVICE OF DR. HOWARD FOX

VARICOSE ULCER AND ECZEMA: PATHOGENESIS AND TREATMENT

THE treatment of varicose veins has usually been considered as belonging within the domain of surgery. Eczema and ulcer complicating varicosities of the lower extremities are, however, cutaneous affections which may properly be cared for by the dermatologist. The use of the intravenous injection method in place of the surgical brings the treatment within his scope. For our series we have selected for treatment only those patients in whom an actual disturbance of the skin was present.

Pathogenesis.—It is unnecessary to discuss the etiology of varicose veins. Opinions vary as to the relative importance of the suspected factors. Heredity, endocrine disturbance, weakness of the wall and valves of the veins, insufficient perivascular support, intrapelvic pressure, and phlebitis all probably take part. The production of the cutaneous changes, however, is dependent upon the presence of varicose veins and of their attendant trophic disturbances.

The pathogenesis of the eczema or ulcer varies with the type of varicosities underlying it. Homans[1] describes three types of varicose veins: the simple surface varix, the surface varix complicated by incompetent perforating veins, and the postphlebitic varix.

1. In the *simple surface varix* there is a gradual development of incompetence of the valves and a gradual stretching and scarring of the venous wall. There is, therefore, developed an

effective collateral circulation and the varicosity is often confined to the main trunk. In this condition the influences which determine the production of eczema and ulcer are trophic, traumatic, and infectious.

A. Trophic: Trendelenburg[2] showed that in the varicose state when the patient stands erect the venous pressure is not sufficient to fill the superficial veins after they have been emptied. Magnus[3] by use of a Volkmann hemodromometer showed that the flow of blood in varicose veins is centrifugal (away from the heart) and that it does not become directed toward the heart until the patient assumes a horizontal position.

The centrifugal flow in the varicose veins causes venous blood with all of its waste products to stagnate in the superficial tissues of the leg. Due to stasis, edema is produced in the region about the varix. The pressure of the edematous fluid stretches the skin and causes a pressure atrophy of the tissues. More pressure is added by the presence of distended veins, and the greatest stretching of the skin occurs directly over the varix. A further result of the stasis is a deposit in the skin of pigment derived from extravasated and broken down erythrocytes.

These trophic factors diminish the nutrition and resistance of the skin and prevent it from recovering normally from external injuries.

B. Traumatic: The skin of the legs is constantly exposed to external injury which may be thermal, chemical, or mechanical, due either to friction of the clothing or to scratching. Any of these may be sufficient to cause eczema.

In other cases there may be more severe injury which breaks the continuity of the skin, such as trauma or the rupture of a very superficial varix. In these cases conditions are favorable for the formation of a varicose ulcer.

C. Infectious: Once the skin has been broken, infection occurs by invasion by the opportunist bacteria of the skin. The infection does not call out the full defense mechanism as in normal skin, but, because of the diminished resistance, the infected ulcer becomes larger and deeper, to produce in time the typical foul varicose sore.

Usually when a simple superficial varix is present the ulcer "rides" over the varicose vein, because that is the location most favorable for damage to the skin.

2. In the *surface varix complicated by incompetent perforating veins* the disturbance is more profound. Normally blood is returned from the lower extremities by an upward flow in both the deep and the superficial veins. The two systems are joined by a number of perforating veins. These anastomotic veins are provided with valves which normally function to allow blood to pass in only one direction, from the superficial to the deep. In the presence of simple superficial varices the perforating veins may function properly for years. In time, however, they become dilated and their valves incompetent, allowing blood to flow from the deep system to the superficial. In addition, following obstruction to the deep veins, as by femoral thrombosis after pregnancy or typhoid fever, the perforating veins also become rapidly incompetent and allow blood from the deep veins to pass toward the heart through the superficial collaterals.

The flow of blood through the incompetent perforating veins adds a large volume to the already overloaded superficial varices and increases the congestion in the superficial tissues. Edema of the legs increases and the nutrition of the entire leg becomes impaired. Ulcers may form on any location on the leg following trauma and infection. Most often, however, they occur at the sites of the perforating veins, where the flow of blood from the deep veins makes the pressure greatest at the surface. Homans[4] states that in excising such varicose ulcers surgeons usually have found a widely dilated perforating vein entering the superficial varix beneath the base of the ulcer.

3. In the *postphlebitic varix* the valves are suddenly destroyed by thrombus formation along the inflamed wall. The veins are small and firm and have a thick wall and a narrow lumen. Even though they are usually invisible they are just as ineffective in carrying on the superficial return as are large varicose veins. The perforating veins are also incompetent in these cases, the valves probably having been destroyed by the same inflammatory process.

The nutrition of the tissues is profoundly disturbed in these cases and edema is great. The skin and superficial tissues are indurated and scar-like over the whole affected region. Ulcers may occur on any location and are often multiple. They usually develop within a few months following the phlebitis.

Selection of Cases for Treatment.—In examining a patient it is first necessary to rule out phlebitis. Postphlebitic ulcers should not be treated by the intravaricose injection method, nor should ordinary varicose veins that have become the seat of thrombophlebitis be injected. The injection of irritating solutions into recently inflamed veins may cause a spreading thrombophlebitis with possible formation of emboli. If the patient gives a history of phlebitis, if phlebitis is actually present, as shown by areas of erythema, heat and tenderness along a vein, or if the ulcer is surrounded by small, hard, straight, and almost invisible veins, that patient should be rejected. Rest, elevation of the leg, and support may be of benefit in these cases and are certainly much safer.

After phlebitis has been ruled out the incompetence of the valves of the superficial veins should be ascertained by means of the *Trendelenburg test.* With the patient lying along the edge of a table the leg is raised above the level of the heart to empty the veins. The leg is then lowered rapidly to a dependent position. If the veins are varicose they are distended suddenly in this maneuver by the rapid downward flow of blood.

In the next step the condition of the perforating veins is determined by the *constriction test.* With the patient recumbent the leg is raised as before, and then the surface veins are compressed by a bandage about the upper thigh. The same compression may be accomplished by pressure over the femoral trigone at the junction of the great saphenous vein with the femoral. The leg is then lowered rapidly to a dependent position. If the valves of the perforating veins are intact the superficial veins will fill slowly (thirty seconds or more) and will not become tensely distended, because the perforating veins will carry off much of their blood to the deep circulation. If the

perforating veins are incompetent the superficial veins will be filled rapidly by the inflow of blood from the deep veins.

A positive constriction test indicates only that the perforating veins are incompetent, but it does not reveal the condition of the deep veins. This is determined by applying a tight elastic bandage to the entire leg for several hours. If relief is obtained, the case is suitable for treatment. If symptoms become worse in spite of the bandage, the deep veins are obstructed and the case should be rejected. Fortunately deep obstruction is uncommon. In such cases the superficial veins act as collaterals for the flow of blood, and to obliterate them would tend further to disturb the circulation.

In some patients only one or several segments of varicose veins may be seen while the rest are hidden by edema. In these the constriction test may be applied to the individual vein by means of two fingers, as suggested by Goldsmith.[5] With the patient erect, one finger is pressed over the lowest part of the varix and another is moved upward along the vein to press out the contained blood. The upper finger is held in place then, and the lower one removed. If blood does not flow upward steadily from below, the vein is not of any use to the circulation and it may be injected. In some cases there may be an apparent upward flow in which, however, blood is entering the vein from a perforating vein or a collateral. This source of error may be eliminated by applying the test at several levels.

Many patients present a pitting edema of the entire leg which hides the veins so as to make the carrying out of the above tests impossible. These patients should be given a complete medical examination to make certain that the edema is not of cardiac or renal origin. If examination shows the patient to be free from constitutional disease, a tight elastic bandage should be applied to the legs and worn for about a week. This measure serves to rule out a possible obstruction of the deep veins and also to reduce the edema so as to make the veins more available. In the presence of unobstructed deep veins the superficial varices of such patients may be injected.

The urine should be examined in every case. The finding of

albuminuria should be followed by a complete medical examination to determine the presence of renal disease. Patients having advanced nephritis should not be injected.

The presence of diabetes mellitus is a contraindication to the injection treatment unless the disease is under management. In an uncontrolled diabetic the intravenous injection of an irritating solution is apt to be followed by perivenous inflammation and by gangrene.

The blood should be examined for the Wassermann reaction. In the presence of syphilis the patient should be given antisyphilitic treatment. If this produces no beneficial change in the ulcer, the injection treatment should be instituted.

Each patient should be examined for the pulsation in the dorsalis pedis artery of both feet. The absence of the pulse may indicate the presence of thrombo-angiitis obliterans. Such patients should be rejected because in them injections may cause gangrene.

Large and deep fibrotic ulcers, even those in which a periostitis is present, are not a contraindication to the injection treatment. Neither does advanced age of the patient, in the absence of the contraindications given above, prohibit injections. In all of these relief is obtained and in many the ulcers are completely healed by this method. No other form of treatment can promise more to such patients.

Technic.—Sufficient work has been done by others to show that obliteration of the varicose veins is in itself effective in healing varicose eczema and varicose ulcers. We have, therefore, not attempted to make of our work a scientifically controlled experiment, but have endeavored to relieve our patients of their disorders as rapidly as possible. To that end we have supplemented the intravaricose injections by cleansing the ulcers often with ether, by applying Lassar's paste locally, and by adding support by the use of an elastic bandage which is worn constantly when the patient is up.

1. *The Solution.*—We have confined ourselves to the use of sodium salicylate for injection. Linser, Sicard, Genevrier, Kausch, Nobl, McPheeters,[6] and others have obtained good

results with sodium chlorid, sodium salicylate, quinin and urethane hydrochlorid, calorose, glucose, and various salts of

Fig. 146.—Before treatment.

Fig. 147.—After seven injections.

mercury. At first we employed a 20 per cent. solution of sodium salicylate and found it satisfactory for obliterating the smaller

varices. We soon changed to the use of the 30 per cent. solution, and with it we have been able to obtain more rapid results.

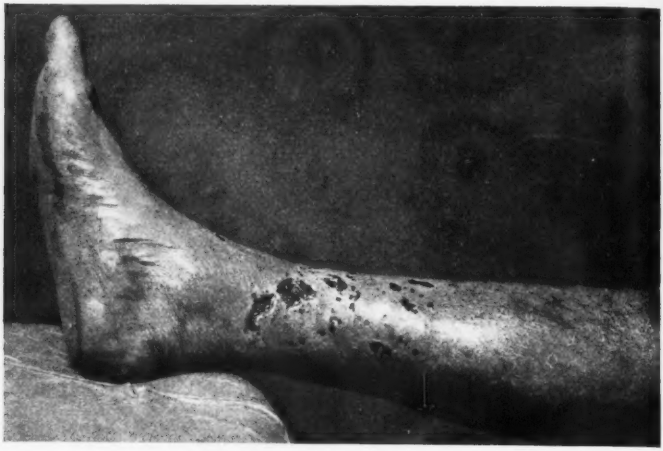

Fig. 148.—Before treatment.

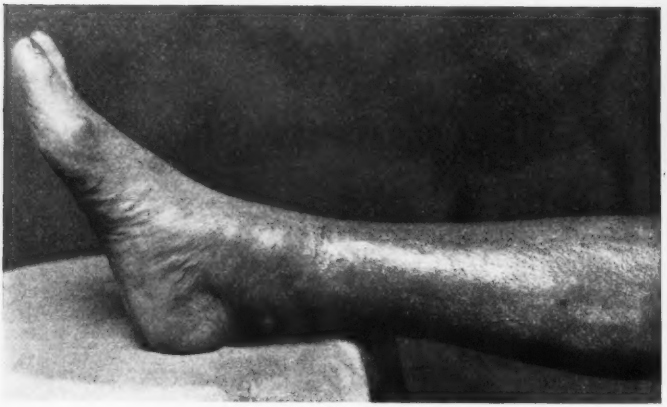

Fig. 149.—After eight injections.

Varices which are not obliterated by a solution of this concentration should be injected with a 40 per cent. solution. Until

now we have not found it necessary to employ this concentration, but it, as well as a 60 per cent. solution, has been used by others with safety. The solution may be obtained in ampules in several

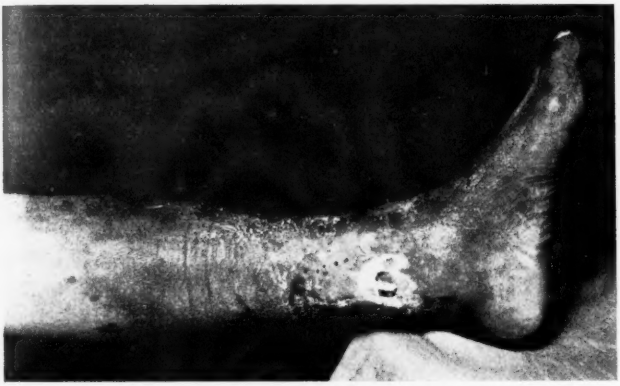

Fig. 150.—Before treatment.

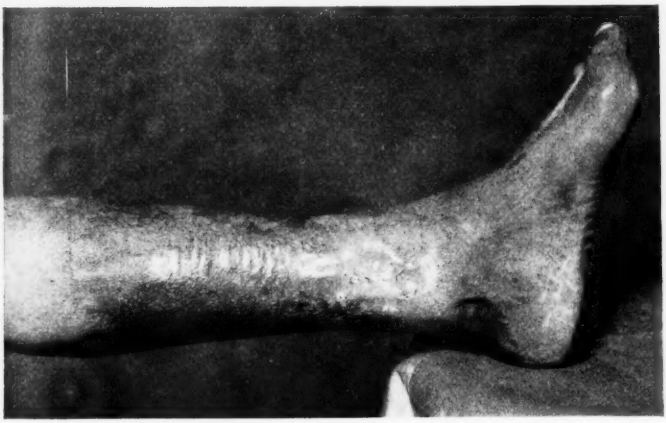

Fig. 151.—After four injections.

strengths, or it may be prepared by dissolving chemically pure sodium salicylate in distilled water in the desired concentration, filtering and boiling before use.

2. *Instruments.*—We are using 10-c.c. glass syringes and steel needles of 24 to 26 gauge and $\frac{3}{4}$-inch length. The needles should be well sharpened and have a short bevel. No tourniquet is employed.

3. *The Injection.*—The patient stands on a high chair which is provided with a high cross-bar to be grasped by him for support. The operator sits before the patient on a stool which should be low enough to make his position comfortable. The veins are distended sufficiently by gravity with the patient standing to make a tourniquet unnecessary.

The vein to be treated is selected and its course is determined by careful palpation. The overlying skin is then cleansed with alcohol. Before puncturing the skin the operator should make certain in every case that his needle is not plugged and that his syringe is in good working order. The needle is then inserted into the vein along its course, but always pointing in an upward direction, until a return flow of blood indicates that the bevel is within the lumen. The needle is then advanced slightly farther within the vein. The entire bevel of the needle must be inside the lumen of the vein so that none of the solution will be injected into the vein wall or the perivascular tissues. Should the distal wall of the vein be perforated during the insertion, even though the needle is drawn back to bring it totally within the lumen, the solution should not be injected, for some of it may leak out through the distal puncture. In such cases the needle should be withdrawn and should be reinserted at some other point. Only after the operator is certain that he has entered the vein correctly should the solution be injected. The injection should be rapid, though not sudden enough to rupture the vein, and pressure should be released a few times during the procedure to make certain that the needle has not been moved out of the vein. With the needle pointing upward, merely releasing the pressure will enable the piston to move back spontaneously to produce a return flow of blood.

When the injection has been completed a wad of cotton or gauze is placed over the puncture and, as the needle is withdrawn, it is pressed down to prevent leakage of the solution from

the vein. This pressure should be continued for several minutes or it may be sustained by fastening the wad to the skin with a strip of adhesive plaster.

During the injection the site should be watched carefully for ballooning or blanching and the patient should report the onset of any burning or stinging sensation at the site. Any of these indicate that the solution is getting into the perivascular tissues and necessitate an immediate halt of the injection. Before injecting it is advisable to draw back into the syringe about 1 c.c. or more of blood. In this way the first fluid to enter the vein will be the patient's own blood and, should it infiltrate the subcutaneous tissues, no harm will be done.

Most patients experience a more or less severe cramp following each injection of sodium salicylate. This comes on about a minute after the injection and is probably caused by the irritation of the intima by the solution. The cramp is not localized at the site of injection, but it radiates down along the course of the injected vein. It is best to have the injection completed and the needle withdrawn before the onset of this sensation, as emotional patients are apt to move the leg about when in pain. With the 30 per cent. solution the cramp lasts about thirty to sixty seconds and is usually not severe, while with greater concentrations of the drug it is more intense.

4. *Method of Procedure.*—We begin the treatment by injecting 3 to 5 c.c. of the 30 per cent. solution into the vein leading upward from the eczema or ulcer, at a point about 3 or 4 inches above the lesion. If the case is one of eczema we apply Lassar's paste locally on a piece of gauze and then bind the whole leg with an elastic bandage. An ulcer, however, is cleansed with ether at each visit and then Lassar's paste is applied, followed by tight bandaging of the whole leg. The patient is allowed to leave as soon as the injections are finished and his leg is bandaged. The dressing of Lassar's is changed by the patient daily and the elastic bandage is worn continually while he is up, being applied before he leaves his bed in the morning and removed in bed at night.

Only one injection is made on the first visit so as to determine the extent of sclerosis produced. Injections are then made

twice a week and an endeavor is made to obliterate all the varicose veins as rapidly as possible. Several veins may be injected at one visit, but not more than 5 grams of sodium salicylate (about 16 c.c. of 30 per cent. solution) should be injected at any one treatment. The amount of solution to be used for any individual injection will depend largely on the operator's judgment. A small superficial varix may be obliterated by 1 c.c., while a large well of blood may require 10 to 15 c.c. of the solution.

At first the veins above the ulcer are injected, the successive injections going upward away from the lesion, even to the varices of the thigh. When these have been obliterated, the veins below are treated similarly. At times a single injection will not obliterate a segment of a vein. The same segment should be reinjected after one or two weeks, with a stronger solution if necessary, until it becomes solid.

In several patients we found small superficial varicose bulbs bulging beneath a very thin skin and apparently ready to rupture. In each of these we injected 1 to $1\frac{1}{2}$ c.c. of the 30 per cent. solution, followed by the application of a tight bandage. In every case the bulb was rapidly sclerosed and obliterated and after a few days was difficult to find.

After all the varicosities have been obliterated, and often before, the ulcer or eczema will heal very rapidly. The application of Lassar's paste may be stopped as soon as healing is complete. The use of the supporting bandage, however, should be continued for at least a month after the last injection.

Complications.—The complication which is most greatly feared is embolism. The series of Sicard,[7] with over 300,000 injections of sodium salicylate without a single embolus, shows that the fear is groundless. The safety of the method lies in the changes produced within the vein. Sodium salicylate does not coagulate blood. It acts merely as a local irritant to produce a chemical phlebitis. The cells of the intima proliferate, fibrin is deposited along the wall, and a firm and adherent thrombus is formed. The venous wall becomes infiltrated by leukocytes and in time the whole vein becomes organized into a solid fibrous

cord. This process usually takes from one to several weeks for its completion. McPheeters and Rice[8] have collected from the literature reports of seven deaths following the injection treatment. In all of these, however, either coagulants were used or solutions other than sodium salicylate which apparently did not produce an adherent thrombus.

The only danger of embolism lies in giving injections when phlebitis is present or in introducing bacteria along with the injection. The resulting infectious phlebitis may spread along the veins without any limit and infected emboli may be thrown off into the circulation. The chemical phlebitis following sodium salicylate occurs only in those locations in which the solution is concentrated enough to irritate the intima. When the solution passes the saphenofemoral junction to enter the femoral vein, or through the perforating veins to enter the deep veins of the leg, it becomes diluted so rapidly by the active flow of blood that it is rendered innocuous. Since it has been shown by Sicard and Gaugier[9] that active muscular movement of the calf of the leg causes suction from the surface toward the deep veins, it is advisable to perform the injections with the patient standing rather than recumbent. The suction produced in the standing position will bring the solution into contact with the perforating veins and may help to obliterate these if they are varicose. There have been no reports of deep vein thrombosis as a complication of sodium salicylate injections.

The most frequent complication following injection is the infiltration of the perivascular tissues. This should never occur with a careful technic. Should any of the solution be injected outside the vein, severe inflammation may be averted by injecting about 5 c.c. of physiologic saline solution subcutaneously and by massaging the infiltrated zone. Forestier[10] states that in a large series of cases he has never seen a slough produced by infiltration with sodium salicylate. This accords with our experience in the comparatively small series of 425 injections.*

* Since this article was written we have encountered one case in which a small slough was produced by an extravenous injection of sodium salicylate solution into the thigh. The resulting ulcer healed within six weeks.

The cramp-like pain experienced by most patients is not a true complication and it cannot be avoided. Certainly it is less unpleasant than the complications which might follow the use of the less painful drugs.

Emotional patients may experience faintness, especially during the first injection. This is merely a nervous reaction and is of no importance.

Results.—The injection method is designed for the ambulatory patient. It enables him to continue his daily activities while under treatment. It offers another advantage over surgical procedures in that it enables the operator to begin treatment of the veins in the presence of infected ulcers.

The pains and aches and the sensation of heaviness in the leg are among the earliest symptoms to disappear. Many patients state that the first injection has brought them sufficient relief to enable them to enjoy the first complete night's sleep in months.

As the varicose veins are obliterated, the edema of the leg subsides and the nutrition of the tissues is improved. The eczema or ulcer, no matter how long present, is usually completely healed after a few weeks of energetic treatment.

Summary.—1. This report is based on results obtained in a series of 60 cases, comprising in all 425 individual injections.

2. The development of varicose eczema and varicose ulcer depends on trophic disturbances secondary to the presence of varicose veins.

3. Obliteration of the varicose veins by injecting an irritating solution, supplemented by supporting the leg by an elastic bandage, causes rapid healing of the eczema or ulcer.

4. Sodium salicylate in the form of a 30 per cent. solution has been found to be an effective and safe sclerosing agent.

5. Postphlebitic ulcers and ulcers in the presence of deep thrombosis, cardiac or renal disease, uncontrolled diabetes mellitus and thrombo-angiitis obliterans should not be treated by this method.

6. The injections are made with the patient standing and without the use of a tourniquet.

7. No emboli have been reported following the use of sodium salicylate.

8. The injection treatment is ambulatory, safe, and effective in causing a disappearance of symptoms and a rapid healing of the varicose eczema or ulcer.

We are grateful to Professor Howard Fox for the opportunity to engage in this work and for supplying us with the photographs. We desire also to thank Dr. S. J. Fanburg for much valuable aid.

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CLINIC OF DR. HAROLD R. MERWARTH

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TUMOR OF THE VERMIS CEREBELLI PROJECTING INTO THE FOURTH VENTRICLE

THIS case is presented because of its many unusual features, and to create a real atmosphere of "brain tumor mindedness" with reference to our cases. As has been said of pernicious anemia, here, too, this general statement may be made: "the incidence of the disease is a good deal the matter of keenness on the part of the practitioners of any district." Unfortunately the diagnosis of cerebral neoplasm frequently presents many difficulties, and although we may sow the seed of suspicion it is often impossible to reap the fruits of confirmation. Nevertheless, as proved by the increasing percentage of brain tumor diagnoses in statistics of postmortem material, it is our firm conviction that in many instances the breath of this suspicion has never been drawn, where subsequent events have proved that more credence should have been placed in its possible occurrence. It may be that the thought is not liberated because of the faulty attitude of the physician as to the apparent hopelessness of such a diagnosis, and the constant suppression of this diagnosis because of this misconception delays the unraveling of the case.

Case I.—Male, white, aged fifty-two, bookkeeper by occupation.

First seen January 4, 1928 (Brooklyn Hospital Dispensary). At that time the complaints given by the wife and patient together were:

1. Severe headaches.
2. Unsteadiness in walking.
3. Abnormal drowsiness.

Past History.—The patient has been subject to headaches off and on for thirty-eight years. They were located in the forehead. He awoke in the morning with headache, which usually lasted until he went to sleep. At times headaches were accompanied by flashes of light in the form of rings, crescents, and zigzags which usually lasted about twenty minutes. The headaches usually occurred about twice a month.

On questioning he states that no member of his family has ever had such headaches.

In 1901, following the taking of McFadden's health cure, he became free from headaches. The free interval lasted up to 1917, when they recurred about once every three months. For a period of six years, 1919–1925, he was entirely without them.

In 1925 the attacks of headaches came back. They began about noon and were accompanied by "zigzags," nausea, and occasional vomiting. The tips of the fingers of his right hand became numb for the first time, the numbness lasting for about twenty minutes. Such attacks came off and on up to February, 1927, at which time a change occurred and his present illness began.

(Up to this point the headaches seem to be definitely migrainous attacks. Their periodicity, the intervals of normalcy, the associated symptoms of nausea, vomiting, paresthesia in one hand, and the accompanying ocular phenomena in an individual otherwise well suggest this opinion.)

Present Illness.—About February, 1927 the attacks of frontal headache increased in severity and in frequency. Bending over increased the intensity of the pain in the forehead. The pains did not radiate, were sharp in character, and were felt as though deep in the head.

The pains continued in this fashion up to October, 1927. At this time he became abnormally drowsy. On one occasion he fell sound asleep at his desk. As a result of his drowsiness and a distinct decrease in his ability to do his work he lost his job.

He yawned frequently. At times hiccoughing was very pronounced. He felt very dizzy at times, particularly on bending over.

About November, 1927 it was noticed that he had difficulty in walking. He even complained of some uncertainty in stepping. At times he seemed to list to the left. This difficulty—slight at first—has become more evident.

Although he has always been emotional, since the onset of his present trouble he has cried frequently without provocation. In December, 1927 the attacks of headache were extreme. Movement of the head seemed to aggravate them. On two occasions he lost control of his urine.

To questioning he claims that he cannot remember clearly. Figures confused him, although he had been adding figures all his life as a bookkeeper. His wife volunteered that he became confused easily. Although he had always treated her with consideration, recently he has become increasingly irritable.

On January 11, 1928 he was admitted to the Brooklyn Hospital, medical service of Dr. W. H. Lohman, with the diagnosis of brain tumor.

Physical Examination.—Male, approximately fifty years of age, with a rather striking, red, constantly flushed face. He lay in bed with both eyes closed. He seemed drowsy, but could be easily aroused. The eyes were drawn as if he were in pain.

There were no irregularities or deformities in the calvarium. No outstanding tenderness was elicited. Even while lying in bed the patient tended to hold the head rather steadily forward. The gaze was directed to the ceiling or the eyes were closed.

When walking he carried himself erect, the head held high and fixed. He seemed to walk with difficulty, carefully measuring each step. At times he swerved to his left. No Romberg evident.

There was a slight tremor of both hands, left greater than right. There was no ataxia and no asynergia. No adiadokokinesis. No awkwardness in skilled tests. No drifting. The heel-to-knee test and the toe-to-object test were well performed.

Reflexes.	R.	L.		R.	L.
Biceps	2	2 plus	S. P.	1	1
			K. J.	1	2
Triceps	2	2 plus	A. J.	2	2
			Bab.	0	?
Abdominal	0	1	Plant.	p	0

Muscle Strength.—There was no demonstrable weakness of the arms or legs.

Sensory.—All modalities unimpaired.

Cranial Nerves.—Two.—Both nerve heads showed a normal physiologic excavation, but were suggestive of an early glaucomatous haziness. Both eyes showed an early and general arteriosclerosis, more marked in the left eye. There was concentric contraction of both visual fields.

Three, Four, Six.—Both pupils reacted sluggishly to light. There was a very slight internal squint in the right eye. There was no nystagmus.

Five.—No corneal hypesthesia.

Seven.—No facial weakness, particularly no left lower facial.

Eight.—No gross disturbance of hearing.

Nine, Ten, Eleven, Twelve.—No speech defect. Tongue protrudes in the midline.

Blood-pressure.—120/76. Pulse 90. Respirations 22. Temperature 99.5° F. January 12, 1928: Spinal puncture performed. Pressure reading 24 mm. Hg. mercury manometer. Fluid clear. Cells 0; sugar retention normal; globulin 0; Wassermann negative.

Blood Wassermann negative.

Urine—albumin 0; sugar 0; microscopic negative.

Blood.—Red blood-cells, 5,200,000; hemoglobin,78 per cent.; white blood-cells, 7300; polymorphonuclears, 74.

Chemistry.—Urea, 62.9 mg.; creatinin, 3.57 mg.; sugar, 119 mg.

January 16, 1928: Spinal puncture repeated. Showed 19 mm. of mercury pressure.

Tests for food sensitivity were negative.

x-Ray of Skull.—No definite pathology of the small bones seen. The bones are rather thin, and an area at the vertex is

especially thin. The sella turcica is a little small and almost closed over. Pineal body is calcified.

January 20, 1928: Vestibular Tests.—"Spontaneous past-pointing of the left hand to the left. Reverse past-pointing of left hand on turning patient to the left. Spontaneous nystagmus on looking to the *extreme* left, but none on looking to the right, up or down. Excessive vertigo on turning patient either to the right or the left. It was impossible to turn more than five times because of the excessive vertigo. Excessive vertigo also resulted after caloric stimulation of the vertical canals."

January 28, 1928: Spinal fluid pressure 50 mm. mercury. Ten c.c. removed, reducing the pressure to 10 mm.

February 1, 1928: The patient seemed to improve under rest, the headaches and spells of dizziness being relieved. In view of his improvement following spinal puncture, the absence of choked disks, evidences of retinal arteriosclerosis, the negative *x*-ray of skull, and the long duration of his symptoms the patient was discharged with a tentative opinion of arteriosclerosis.

February 10, 1928: He returned to the clinic with a recurrence of his previous complaints. He had a few vomiting attacks associated with the headaches and dizzy spells. Confusion was more marked. He seemed to incline to the left on walking. Reflexes on the left were increased. Bilateral tremor of the hands was present. The fundi were clearly outlined.

March 22, 1928: He had several seizures, characterized by sudden loss of consciousness, complete rigidity, pallor of the face, and no convulsive movements. At the time of the first seizure his wife thought he had died. The fundi were still normal.

April 5, 1928: Because of an increasing confusion, the occurrence of incontinence at night, with two more rigid seizures, it was deemed advisable to readmit him to the hospital for further study. The physical findings were the same as on previous visit, except for a greater increase of the reflexes on the left. The fundi were normal. No nystagmus present.

April 12, 1928: Both visual fields were more generally contracted than at the previous visit. Pressure of spinal fluid was 24 mm. mercury. Twenty c.c. of spinal fluid were removed.

April 18, 1928: The patient awoke with a frontal headache. Spinal puncture was repeated. Pressure 24 mm. mercury. Very little fluid obtained.

April 19, 1928: He awoke with a severe frontal headache, nausea, and projectile vomiting. He saw double for about twenty minutes. At this time he showed a definite incoördination of both upper extremities L>R. Both patellar reflexes were increased. Permanent clonus of the right foot noted. For the first time there was slight vagueness of the outlines of the optic disks, especially in the right eye. He complains of hiccoughing and seeing double.

At this time a definite diagnosis of a tumor in the posterior fossa was made—a tumor invading the cerebellum. His condition became worse so rapidly that a suboccipital exploration was out of the question.

April 20, 1928: A corpus callosal puncture was performed to relieve the intracranial pressure. Following this the patient's condition became progressively worse and on April 22, 1928 he died with a terminal hyperpyrexia of 107° F.

Autopsy Findings (James W. Denton).—*Brain.*—On removing the skull cap the dura over the convexity is of normal color except about the opening through the skull cap. The dura is neatly sutured where it has been opened. The brain is of normal color, but the gyri appear somewhat flattened and the fluid in the pia appears somewhat decreased in amount. On pulling apart the frontal lobes a linear laceration of the corpus callosum 1 cm. long and 0.5 cm. wide appears. This is just to the right of the midline and about 1.5 cm. back of the anterior border of the corpus callosum. There is a normal amount of fluid beneath the tentorium cerebelli. The soft meninges about the sylvian fissure are somewhat opaque and grayish-white in color. The meninges over the rest of the brain appear of normal color and thickness. Sections through the lateral borders of the corpus callosum into both lateral ventricles show that both are markedly dilated. The opening in the corpus callosum leads down into the right ventricular space just anterior to the foramen of Monro. There is a small but deep laceration in the floor of the right lateral

ventricle. The third and fourth ventricles are greatly dilated. The aqueduct is open.

A section down through the vermis discloses a round tumor in the midline of the vermis cerebelli. It is about 3 cm. in diameter. It spreads out with well-circumscribed borders into both lateral lobes of the cerebellum. The tumor is readily visible externally on the inferior surface of the cerebellum, as it has extended down into the foramen magnum, but without any break in the pia of the cerebellum. On section the tumor is

Fig. 152.—Photograph, natural size, showing the tumor invading the fourth ventricle, and the tremendous dilatation of the aqueduct and third ventricle.

somewhat lighter in color than the surrounding cerebellar substance and firmer in consistency.

The medulla oblongata has been pushed forward by the tumor and is compressed against the anterior surface of the tumor. There is a distinct pressure cone, from the jamming down of the medulla oblongata into the foramen magnum.

Note.—No evidence of tumor was found in any of the organs except the brain. The growth in the brain is clearly of cerebellar origin (vermis).

Histologic.—Sections of the tumor of the vermis projecting into the fourth ventricle show that it is made up of generally spindle-shaped cells of varying sizes and strands and bundles of fibrillæ. In places tumor cells form well-marked alveolar arrangements with respect to the fibrillæ, the fibrillæ in many places forming spherical masses surrounded by the tumor cells.

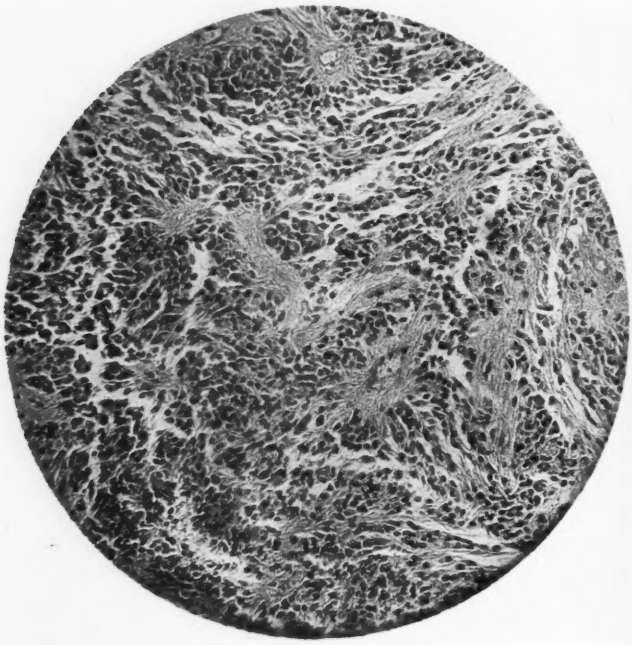

Fig. 153.—Low-power photomicrograph of the tumor which shows it made up of bundles of fibrillæ with indefinite retention of rosettes.

The nuclei are of medium size and very rich in chromatin, and there is but scanty cytoplasm about the nuclei. The fibrillæ are generally quite coarse and in places form wide bands of pink staining material, but this is looked upon as a secondary change in the fibrillæ. The growth, from the great number of the fibrillæ and from the marked hyalinization of the larger bundles,

is evidently a very slow-growing tumor. The diagnosis is a neurocytoma.

Discussion.—This case verifies the contention of others, that the location of head pain is unreliable for localizing purposes. With very few exceptions does the headache bear a relationship to the site of the intracranial lesion. In this particular case the

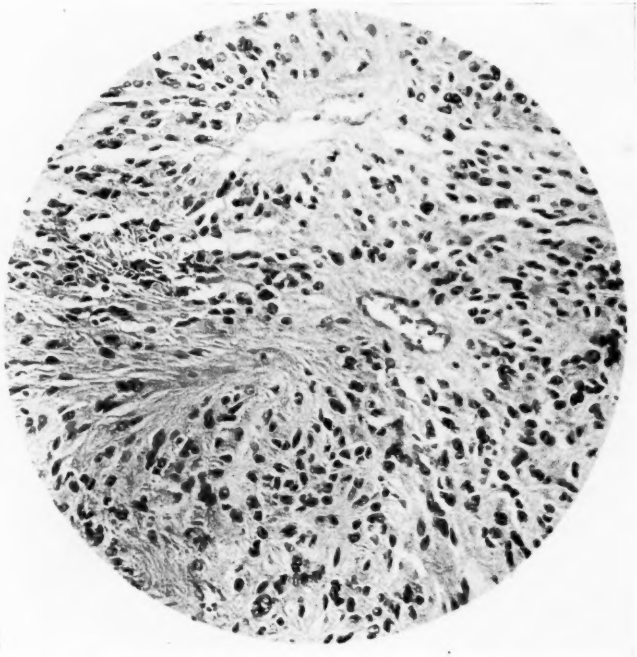

Fig. 154.—High-power photomicrograph showing essentially same features as Fig. 153.

headache was continuously frontal in location, yet the neoplasm was located in the posterior fossa.

As noted, the possibility of migraine had been suspected because of the long duration of the headaches. Severe headaches occurred over a period of thirty-eight years, happening once or twice a month, frontal in character, and accompanied

by visual scotomata. There seems to be no doubt that the headaches for most of these years was of a migraine character, as it is hardly likely that a brain tumor could exist for thirty-eight years in any location and particularly in the vermis cerebelli. There was a change in the severity of the headaches two and a half years before his admission to the hospital, with an intensification of the scotomata, and with paresthesiæ of one arm, very characteristic of the migraine seizure. The nature of the tumor, a notably slow-growing neoplasm, so located that it could easily cause a temporary interference in the subarachnoid flow, could explain headaches occurring over a brief period of years. It is an interesting point of speculation, whether the latter headaches were due to transient increases of intracranial pressure due to a block, or were genuinely of a migrainous pattern, the developing neoplasm acting as a burning match and rendering the cerebral mechanism ore liable to an explosion, known as migraine. In any event, in every case of so-called "migraine" the possibility of intracranial neoplasm must be considered very seriously, which point is emphasized by the dénouement in this case.

A change in personality had occurred. The patient had become forgetful, of recent events particularly, so much so that he lost his job. Also he became careless in taking care of his person. An increasing irritability had been noted. A degree of melancholia with crying spells colored the picture. A change of personality in intrinsic disease of the frontal lobes has been regarded by many writers as of great significance. In this case the change in personality, slight but definite, was due undoubtedly to the increased intraventricular pressure probably exerting a general pressure on the frontal terrain—and not a local phenomenon—per se. At the postmortem a tremendous dilatation of all ventricles and the iter suggested a process of long standing and so gradual in onset that an adjustment had been made.

The triad—yawning, hiccoughs, and drowsiness—present over a long period in a patient without choked disks indicated nothing but a generally increased intracranial pressure. By some yawning is supposed to point to local disease in one of the

frontal lobes, more especially in those cases where other localizing signs are absent. If so, it should have been of aid in this patient with few signs and no choked disks.

Of casual interest is the lack of ill effect after withdrawal of spinal fluid. Ordinarily, in instances of suspected neoplasm in the posterior fossa it is a rigid rule that the withdrawal of spinal fluid by the lumbar route should be done with great caution or not at all. This patient had four such taps with no extraordinary precautions being taken. The patient actually seemed to benefit by the first two taps, due to the reduction of intracranial pressure. This unusual occurrence can be explained anatomically by the fairly fixed position of the neoplasm, which was firmly embedded in the cerebellomedullary substance and not easily influenced by the withdrawal of fluid from below. The medullary pressure cone found at postmortem proved that the pitcher had gone to the well once too often.

Despite the location of the neoplasm, and the suggestive evidences of intracranial pressure, such as headaches, yawning, drowsiness, hiccoughs, and occasional incontinence papilledema never appeared until the last forty-eight hours, when the condition of the patient was precarious and the disks definitely choked. Thus one of our most valued aids in the diagnosis of brain tumor really never appeared to aid us.

It is noteworthy that the *x*-ray failed to show real evidences of increased intracranial pressure, such as "convolutional atrophy" and erosion of the posterior clinoid processes. It is true that the skull as a whole was generally thin.

There were three hints of localizing value in this case.

1. Gait: A tendency to a wide base with head held rigidly erect in a stiff military posture. There was just a very occasional listing to the left. This head posture is supposed to be very suggestive of a foreign body invading the fourth ventricle.

2. The "spells" when carefully analyzed later were apparently extensor fits. The patient was in coma, pale; teeth were clenched; limbs were rigidly extended. At no time were there convulsive movements. These "spells" are decerebrate rigidity seizures.

3. The caloric reactions suggested invasion of the left cerebellar hemisphere.

Summary.—A case of a tumor of the vermis cerebelli invading the fourth ventricle has been presented, showing several unusual features.

1. Complete absence of choked disks until just before death.

2. Suggestive evidence of intracranial pressure increase, because of headaches, vomiting, yawning, hiccoughs, drowsiness over a long period without changes in the fundus oculi and without *x*-ray changes.

3. Successful withdrawal of large quantities of spinal fluid on three occasions with apparent benefit to the patient and no untoward affects.

4. The addition of a tumor syndrome to a classical migraine history, with evidences of arteriosclerosis to further confuse the picture.

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THE RÔLE OF THE LEUKOCYTES IN INFECTION

THE blood-stream is a reservoir that receives into its moving current all the cellular products of the formative organs of hematopoiesis. Thus, by careful morphologic examination of this medium we see, reflected as in a mirror, the sum total or end-result of the normal physiologic continuous destruction and replenishment of its formed elements. With any irritation of the bone-marrow, lymphatic organs, or reticulo-endothelial system, be it toxic or infectious, an immediate and specific reaction is to be observed in their respective cellular constituents. This reaction is not a simple chemotactic call to the polymorphonuclear neutrophils to stem the tide of infection, but a biologic chain of events in which all three cellular components of the leukocytes actively participate. As each system is called into action, the others recede into the background, only to reappear the moment they can be utilized to the best advantage.

Although even in Grecian times it was known that the blood plays an important rôle during infections, it was only toward the latter part of the 17th century that any of the leukocytes were discovered. Leeuwenhoek, in 1673, was the first to discover the lymphocytes in the lymph vessels. Hewson later described leukocytes in the blood. Max Schultz and Virchow then differentiated lymphocytes from large leukocytes. In 1868 Newmann discovered that bone-marrow is the source of the red blood-cells, and two years later established its importance in the genesis of leukemia. Forty years ago Ehrlich, by his epoch-making discovery of blood stains and methods, made possible the first reliable subdivision of leukocytes.

Until recently hematologists were divided into two camps: the unitarians, led by Maximoff, Weidenreich, Downing, etc., who claimed that the lymphocyte was the basic cell, and the dualists, led by Ehrlich, Naegeli, Pappenheim, etc., who claimed two systems—the granular and the non-granular. Thus we had the lymphocyte from the lymph-gland, and the granulocytes and monocytes from the bone-marrow. In 1898 Ehrlich placed the monocyte with the non-granular cells, but believed it to be myeloid in origin. He thought that it differed from the granulocytes only by its special granules. Pappenheim placed the transitionals and large mononuclears in one class, called the monocytes. He showed that the granules of the monocytes were in no way connected with those of the neutrophils. Thus we had the monocyte, claimed by both the unitarians and the dualists. Of late a new school has come into being—the triolistic school. The literature dealing with the monocyte and its supposed mother tissue, the reticulo-endothelial system, is truly voluminous in its extent. This hitherto neglected cell has now become the subject of marked controversy. Schilling, the leader of this last school, believes the monocyte to be the representative of a separate system. He has described cases of monocytic leukemia and shown cases of marked monocytic hyperactivity in malignant endocarditis. Aschoff and Kiyono, in 1913–1914, compiling all the previous work done on this subject in conjunction with their own, evolved that system which we now know as the reticulo-endothelial system.

To appreciate fully any changes that may be encountered due to irritation of the blood-forming organs during infections, one should be conversant with the normal blood-picture and its physiologic variations. Careful observations of repeated hourly blood examinations have shown that the number of leukocytes seems to fluctuate considerably and with a definite rhythm. Thus, it has been found to have two tides in twenty-four hours, one in the afternoon and the other somewhat past midnight. It was also found, contrary to previous beliefs, that these curves were consistently present and were apparently independent of, and unaffected by, normal exercise and digestion. Intense or

prolonged physical or mental exertion, however, was found to cause an intense leukocytosis due to a neutrophilia. Within these normal limits the leukocytes remained remarkably constant. Under normal conditions the three leukocytic constituents mature in their respective mother tissues and are sent into the rapidly moving blood-current. They perform their physiologic functions, complete their life cycles, and then are automatically withdrawn from the circulation. Thus a definite percentage of the total number of leukocytes is furnished during every minute, to replace the same number withdrawn, resulting in a constant leukocytic level.

The normal leukocyte count for the adult after the age of fifteen ranges between five and nine thousand. The differential is usually composed of 3 to 5 per cent. staff neutrophils, 60 to 65 per cent. segmented neutrophils, 20 to 30 per cent. lymphocytes, $\frac{1}{2}$ per cent. basophils, 3 to 5 per cent. eosinophils, and about 4 to 6 per cent. monocytes. This count varies in infancy and in old age. The newborn infant, for the first few days, may have a leukocyte count as high as 20,000. During its nursing period the count generally drops to about 13,000. The percentage of lymphocytes is usually between 60 and 70. As the age of the child increases, the number of leukocytes diminishes so that at about the age of puberty it has reached normal. Accompanying this change there is a corresponding decrease in the lymphocytes to their normal ratio of 20 to 30 per cent. It has been my experience that the percentage of lymphocytes in old age has a tendency to rise to about 40 to 50. This may be a sign of the fatty replacement of the cellular structure of the bone-marrow, with its gradual weakening. It is also possible that it may be due to an increased catabolism continually going on in the age.

What controls this perpetual renewal and withdrawal of these cellular elements? This problem is stupendous in its possibilities, but it is not the object of this paper to enter into its discussion. Clinical observations seem to point to some interrelation between the spleen and the bone-marrow, which may be internal-secretory or hormonic in mechanism. Other internal

secretions may also play an important rôle by their effect on these two organs.

What happens to the normal blood-picture with the advent of a foreign substance of infectious or toxic character? What changes occur with the establishment of a focus in an organ of the human being? We find it a very sensitive indicator, for whereas before the irritation the blood-count was remarkably constant, with the introduction of this foreign body there is an immediate change in the number and character of the respective white blood-cells. According to Virchow, Arndt, and Schultze this change is, in reality, a definite chain of biologic events. With the entrenchment of any infectious force at its portal of entry in the human being, there is usually both a local and a general reaction. These reactions will depend on two important factors: first, the severity of the infecting organism and, second, the condition of the patient and his ability to defend himself against it. The first cell to answer the emergency call for protection is the neutrophil.

This phenomenon of shock troops to meet and destroy the invading force can be called the *neutrophilic or combat phase of infection* (*Neutrophil oder Kampfphase* of Schilling). When any tissue is infected, it becomes the site of local inflammation, with a resultant reaction that can be observed and followed in the blood. Ordinarily, organisms that have succeeded in penetrating past all the natural barriers of defense and have reached the inner tissues find it impossible to multiply owing to the antagonistic, antibacterial tissue juices. However, when the bacteria are of sufficient virulence or the resistance of the host is impaired, rapid growth will result. As this growth progresses, the products of its metabolism cause necrosis of the involved tissue. This, in turn, affords the invading germ increased shelter against these tissue juices. As the establishment of the invader becomes evident, the insulted tissue begins its counterattack. All the capillaries, the roads leading to the affected area, immediately widen to allow for the transportation of more blood to the area in need. Arterioles and venules of the adjacent parts are soon also involved. It is then that one sees, in spite of the widening of the

capillaries and the rapid rush of blood, a gradual slowing of the current and a clearing along the capillary walls. Soon the leukocytes appear to hug these walls and finally pierce them to actively immigrate into the zone of conflict. Most of these cells are polymorphonuclear leukocytes. These neutrophils travel toward the infected area in their effort to stop and destroy the invader. If the germs have fortified their positions by surrounding themselves with toxins, some of the neutrophils will deposit themselves between the healthy and the affected parts in an effort to shut off any further advance. In their march many are destroyed, but others pass these dead continuously in their effort to annihilate the invader.

It is quite obvious that as this local process goes on, the blood-picture will definitely reflect the relative strength and progress of both the host and the invader. If the source of irritation is mild, the local condition will be checked speedily, the call on the bone-marrow for neutrophils will be insignificant and the blood-picture will show none or, at best, a slight increase in the number of mature granulocytes. If the irritation is moderate, there will be a productive reaction in the bone-marrow. This will result in a variable increase in the total number of leukocytes due to a neutrophilia. The bone-marrow, however, will have had sufficient time to allow for complete maturation of its product with the result that the number of immature neutrophils will show but a slight increase. In this grade of infection the percentage of staff neutrophils will rise from the normal 3 or 5 per cent. to 10 or 15 per cent. When dealing with a severe form of irritation, we have the firm establishment of an invading organism in the tissue of the host, with the apparent temporary supremacy of the bacteria. In these cases the bone-marrow, either due to prolonged or excessive demands made upon it, or due to the sudden, severe toxic stimulation, yields a marked increase in the number of immature neutrophils due to an apparent interference with the normal maturation of the white blood-cells. The percentage of staff neutrophils in this class usually averages around 20 to 30. Some of the neutrophils will also be found to have granular degeneration of protoplasm.

For the cases in this group the prognosis is doubtful and often fatal unless the source of irritation can be located and eradicated. In the last group, that of very severe irritation, we have that class of extremely virulent organism invading a host with no resistance, resulting in a complete overpowering and absolute inhibition of the bone-marrow. In these terrific infections there is a paralysis of all leukopoiesis in the marrow, with granular degeneration of individual neutrophils in the circulation. Careful morphologic examinations in these cases show a rapid decrease in the number of granular cells. Before the total number has reached nil, the percentage of immature cells may rise as high as 70 of all the leukocytes in the smear. The marked degeneration of both the protoplasm and the solution of the nucleus will make differentiation almost impossible. Death in these cases is inevitable and usually very rapid. This subdivision of neutrophilic reaction is of course very elastic, each group gradually merging into the other. If the infection is very severe, but tending toward eventual recovery, serial examinations, if made at regular intervals, will show all four subclasses during its course. In the first two classes we have what Schilling terms the regenerative blood-picture, or the presence of metamyelocytes among the immature cells that are present. In the third, or severe group, we have the mixed regenerative-degenerative, and in the last group, the very severe, the degenerative with the complete absence of metamyelocytes. Chart 1

Chart 1—Subdivision of Infections—Using per cent. St. as Indicator.

	W. B. C.	Neutrophils. M.	Mt.	St.	Seg.*	B.	E.	Lym.	Mo.	
				Per-cent. 3–5	Per-cent. 60–70	Per-cent. ½–1	Per-cent. 2–5	Per cent. 20–30	Per-cent. 4–8	
Normal.....	59,000	..	..							
1. Mild.....	9,000	..	1	5	68	..	..	20	6	
2. Moderate....	10,200	..	2	10	67	..	..	20	1	
3. Severe.....	28,400	..	1	33	50	..	..	15	3	
4. Very severe..	36,400	..	..	41	47	..	..	10	2	D
	13,000	..	..	79	17	..	..	4	..	D
	4,000	..	..	59	17	..	..	24	..	D

D—died.

shows the leukocyte count and differential to be expected in the various classes of infections.

In class 1, that of mild irritation, there are usually included cases of acute colds of the upper respiratory tract, superficial infections, and cases at the beginning of convalescence. The second or moderate group holds all acute catarrhal conditions of the appendix, gall-bladder, or other viscera, infections of the middle ear with complicating mastoiditis, and infections of the lower respiratory tract. The third and fourth groups are more or less one, the differentiation depending upon the favorable outcome in the third, and exitus in the last. The example of the severe group given in the chart was that of a case of acute purulent appendicitis with perforation, that eventually recovered. The 3 cases cited among the very severe were: (1) Sepsis due to postoperative infection; (2) perforated duodenal ulcer due to peritonitis; and (3) ruptured appendix with peritonitis. All three of these patients died.

The neutrophils, having reached the cite of infection and having performed their function, now call to their aid the monocytes. This results in the *monocytic* or *conquest phase (monozytaere Abwehr-Ueberwindungsphase)*. This phase is by far not as spectacular as the neutrophilic phase. At the onset of acute infections the monocytes gradually disappear more or less, while the immature neutrophils rise in their stepladder fashion until they reach their pinnacle. As the staff cells start to drop suddenly, the monocytic phase begins. Whereas the combat phase may have taken days or weeks, the monocytic or conquest phase takes but a few hours. It appears to be very transient, starting to rise as the staffs drop, reaching its summit quickly, and dropping to make way for the last phase. Due to this transient nature, it is usually missed unless hourly examinations of the blood are undertaken just before, during, and immediately after the crisis.

The presence of this monocytic phase is best depicted during the crisis of a malaria chill. In malaria, owing to the fact that each individual attack lasts in its entirety but a number of hours, and as each phase of the attack can be clearly foreseen, and

lastly, because there are no complicating or interfering features, it is a simple task to observe the full play of the leukocytes as they follow one another in a definite sequence. In paretic patients treated with malaria I was able by frequent blood examinations, taken before, during, and after the chill, to note the neutrophilic phase as it rapidly rose during and immediately after the chill. Then, with the drop in temperature and the sharp decline in the percentage of immature neutrophilic cells, this new phase was ushered in with the sudden appearance of the monocytes. At times the monocytes rose as high as 38 per cent. of the total white count. Increased monocytic activity was also evidenced by the presence of mitotic figures, double nuclei, and active phagocytosis. Malaria-infected erythrocytes were frequently to be found in the bodies of the monocytes. Thus

Chart 2

H. I., male, age forty-eight years, paresis. Condition improved, January 12, 1926.

W.B.C.	Neutrophils. Mt.	St.	S.	Ly.	E.	B.	Mo.	
5000	.3	7	40	45.2	..	.3	4.5	
4800	...	10	57	30	..	..	3	
5800	5	23½	49½	20	..	..	2	Taken during a chill.
5600	13	42	37	5	..	..	3	Taken during height of a chill.
5400	2½	6½	39	14	..	..	38	Taken after the chill.
6200	...	5	52	30	..	..	13	
5900	...	3	38	50	..	..	9	Taken during the intervals.

In spite of the fairly constant leukocyte level, the immature neutrophils, monocytes, and lymphocytes are found to vary, depending upon time taken in reference to the malaria chill.

we find in malaria-treated cases of paresis, immediately following the neutrophilic stage, this transient monocytic stage showing marked hyperfunction of the reticulo-endothelial system. In cases showing a mixed tertian infection where chills follow one another in rapid succession (quiescent interval one to two hours), the staff count would not drop to normal, but having declined slightly would rise again during the next chill. In these cases the monocytic phase will usually be absent until after the second chill.

In my efforts to demonstrate this period of monocytic activity in acute infections, I chose acute lobar pneumonia as the illness most likely to show this relationship. In these cases the onset usually is ushered in with a chill, pain in the chest, and rise in temperature. Inasmuch as the crisis in such cases can usually be expected between the seventh and ninth days, complete daily counts were made, and the percentage of immature neutrophils carefully observed. On the day that the crisis was expected, because of the high point reached by the staff count (usually between 25 and 30 per cent.), and the toxemia of the patient, hourly smears were taken in our effort to include this phase. At no time, however, were we able to demonstrate definitely a monocytic curve. The staff cells would not drop by crisis, as after a malaria chill, but by a rapid lysis. High monocytic counts were found, but not regularly and not in consecutive examinations. Similar experience was also encountered in most other acute ailments. This was no doubt due to the fact that whereas acute infections can clinically be subdivided into their various phases, pathologically there is no period when the disease process is a pure one. Thus pathologic examination of the lung in pneumonia taken at any time during its course would not show one pathologic state, but areas of engorgement, red and gray hepatization, and resolution. Even at the crisis, when the clinical picture definitely shows recovery and convalescence, the lung pathologically shows the same condition. In a malaria attack, however, each phase is clearcut and concise. Therefore the resultant reaction in the blood-stream shows itself as three separate and distinct phases. Figure 155 clearly shows these three periods of leukocytic stimulation.

When a high percentage of monocytes appears in the blood during an acute infection, it usually indicates a crisis with the tendency to the healing phase dominant. In chronic or subacute illnesses, however, monocytosis is a sign of continuation of the infection. This is the case in patients with chronic sepsis, such as subacute bacterial endocarditis, etc. These cases always show a high constant level of immature neutrophils, accompanied by increase in the number of monocytes. The percentage of

lymphocytes may be subnormal, normal, or even slightly increased.

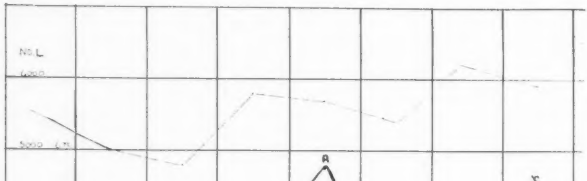

Fig. 155.—Shows definite sequence of neutrophilic, monocytic, and lymphocytic phases.

Chart 3

T. H., female, age thirty-four years, subacute bacterial endocarditis; died.

Date.	R. B. C.	Hb.	W.B.C.	Neutrophils Mt.	St.	S.	Ly.	Mo.	
6/27/27	2,900,000	55	6,800	..	24	51	21	4	Blood-culture—Strep. virid. markedly degenerated.
6/29/27	2,960,000	45	9,400	..	24	60	14	2	N degen. Mo. markedly vacuolated. Transfusion.
7/ 1/27	3,500,000	60	10,400	3	38	48	19	2	N degen. Mo. vacuolated.
7/ 6/27	.....	..	....	..	18	56	18	9	Idem.
7 8/ 27	.....	..	....	2	21	50	15	12	Idem.
7/10/27	.....	..	....	1	32	44	15	8	Idem.
7/18/27	.....	..	....	1	24	35	35	5	Idem.
7/24/27	.....	..	.....	..	36	40	20	4	Idem.

This shows constant level of St. neutrophils with occasional increased per cent. monocytes and normal lymphocytes. Marked constant degeneration of N shows severe impairment of the bone-marrow, and vacuolated monocytes indicate constant hyperactivity and phagocytosis.

In acute infections, the monocyte peak having been passed, the percentage of lymphocytes rises rapidly and stays high until the infection is overcome. Wave C in Fig. 155 shows the pres-

ence of this high peak following the monocytic wave. With the onset of the disease process the percentage of lymphocytes has dropped from the normal 25 to 30 per cent. down to 10 to 15 per cent. or less. All during the neutrophilic stage the number of lymphocytes remained low and started to rise just as the monocytes had begun to drop. The lymphocytes may rise to as high as 50 to 55 per cent. of the total count. This rise is not due to the disappearance of the neutrophil, but to an active stimulation of the lymphatic system. This is evidenced by the presence of plasma cells, Reider cells, and lymphocytes with two nuclei. As convalescence turns into normalcy, the lymphocytes return to their normal level and irritative forms disappear from the blood-stream. If the infective process is not completely eradicated, and the illness continues in a subacute or low-grade form, the lymphocytes will remain high during that entire period. In such instances both the immature neutrophils and monocytes will also be above their normal level. There is one type of acute infection, however, where the percentage of lymphocytes will remain high during the acute stage of the illness and may even rise as the illness progresses. This occurs in cases of acute sepsis with paralysis of the bone-marrow. Here we find a marked leukopenia, often as low as 1000 to 1500 white cells, with 60 to 70 per cent. lymphocytes. The relative lymphocytosis in these cases does not indicate a hyperaction of the lymphatic system, as the total may show an absolute lymphopenia and irritative forms are absent. These cases are often confounded with the so-called "lymphatic reaction," or even with the lymphatic leukemia of the leukopenic form. Agranulocytic sepsis, with total disappearance of all granulocytes, belongs to this group. All of these cases are rapid and fatal, unless the bone-marrow is but temporarily inhibited and not paralyzed.

Discussion.—For many years the interest of the physician in the blood-count was centered about the total leukocyte count and the percentage of polymorphonuclear neutrophils. The lymphocyte was supposed to exert but a passive rôle during any change in the blood-count. The monocyte, just as the basophil and the eosinophil, played but a very minor and unimportant

rôle. It is therefore not surprising that the interest of both the clinician and the surgeon has lagged. Due to the proper interpretation of the blood findings, physicians have been led to feel that the blood examinations have been of value only when they apparently corroborated the clinical findings. Very often indeed were the leukocyte and polymorphonuclear neutrophil counts of no help at all. The teaching that a high leukocyte count with a low percentage of polynuclears indicated a good resistance, and that a low leukocyte with a high percentage of polynuclears indicated a severe infection, is no longer tenable. Careful morphologic examinations of first the neutrophil, then the lymphocyte, and finally the monocytes, have demonstrated that whereas the blood examinations previously had been of no clinical help, they could now offer additional information which was of extreme value in diagnosis, prognosis, and treatment. As these careful morphologic findings revealed the definite value of blood examinations, daily and even hourly observations were undertaken. By noting the changes in the morphology of the nuclei in the neutrophils and the granules in their protoplasm, we found that we could definitely determine the condition of the bone-marrow in its reaction to infection. We could then use this bone-marrow reaction as an index of the severity of the disease process. We then also found that it was not only the neutrophil that was involved in the fight against the foreign invader, but that all three cellular systems participated actively in an orderly fashion at definite times during the infection. Thus, depending upon the stage of the illness, be it the onset, the crisis, or period of convalescence, a fairly definite blood-picture could be expected. What is the significance of the sudden outpouring of monocytes at the crisis in acute infection? What does their persistence in subacute or chronic conditions indicate? Many years ago Metchnikoff, in his theory of phagocytosis, labeled the neutrophil "microphage," and the monocyte "macrophage." The neutrophil was the first cell to appear in the affected area and was supposed to do the actual destroying of the organism. The monocyte, in its capacity of macrophage, would then enter the involved area to carry off the dead and disabled. If the illness is an acute one, terminating in recovery

by crisis, the neutrophils, having stopped and destroyed the invading force, make way for the monocytes, which hurriedly clear away all the large obstruction, so that the lymphocyte may start its healing stage. In cases that tend to be chronic all three of these cells work synchronously. Very little is actually known of the function or action of the lymphocyte. Its presence in chronic conditions such as tuberculosis has brought forth the suggestion that it exerts its influence by means of some lipolytic ferment or enzyme. With this ferment it destroys the fatty capsule of the tubercle bacillus, thus making its destruction possible. Do the azure granules of the lymphocyte have any function? Up to the present time very little has been accomplished along this line. In the capacity of bringing about final restitution of the diseased part by the lymphocyte this lipolytic ferment may be the instrument employed. Very little is known of the function of basophils. They are always found in increased numbers with increased function of the bone-marrow. The eosinophils are definitely linked with the monocyte and always disappear from the blood-stream with the onset of an infection, to reappear at the end of the neutrophilic phase. Of the function of these cells very little is also known.

Conclusion.—Every infection causes a bone-marrow reaction which demonstrates itself as a neutrophilia. This neutrophilia, depending upon the severity of the toxin of the organism, will have a varying number of immature staff forms. It is these cells that can be traced throughout the course of an infection to determine whether the prognosis will be good or poor. *A high staff count does not indicate a fatal prognosis.* It is the continued high level or the steady increase in the level of the staff cells, without the possibility of removing the causative focus, that invariably and almost absolutely spells a fatal prognosis. I have seen staff counts as high as 70 per cent. at the crisis in pneumonia with eventual recovery. With the removal of the purulent focus, the staff count will invariably drop, rapidly or slowly, depending upon the amount of reactive or infective tissue left behind.

In illnesses that end by crisis the monocytes will be found

to follow immediately after the previous stage. With the sharp drop in the staff count the monocytes will suddenly appear into the blood-stream, showing definite signs of hyperactivity. In subacute or chronic infections a monocytosis will indicate the continued presence of the diseased process.

Lymphopenia is present with the onset of an infection. This remains so until the inception of convalescence, during which time it may rise as high as 50 per cent. or more. During chronic illnesses it will be present in varying degrees, with increases in staff cells and monocytes.

Thus all three systems work harmoniously, starting with the neutrophilic or combat phase, followed at the crisis by the monocytic or conquest phase, and ending with the inception of convalescence with the lymphocytic or healing phase.

Before ending this paper there are a few words that I wish to add concerning blood examinations in general. The blood-picture may exceptionally fail you due to some unknown or, better said, unrecognizable reason. One must not feel discouraged and think, therefore, that laboratory examinations are useless. Blood findings must always be considered in connection with the complete findings of the clinician. An outstanding and definite clinical picture can never be negated by negative blood findings, just as outstanding blood findings cannot be disregarded because of lack of clinical signs. Lastly, for the proper evaluation of blood data, frequent serial blood examinations must be taken to allow for recognition of the biologic chain of interaction of all the leukocytes.

CLINIC OF DR. JOSEPH LINTZ

FIFTH AVENUE HOSPITAL

FEVER IN MALIGNANCY

THE belief that malignant growths run an afebrile course is held generally. Yet it happens not uncommonly that instances of neoplasm occur where the earliest and most prominent symptom is a continued or intermittent pyrexia. Many cases are recorded where the true diagnosis was missed because of this continuous elevation of temperature.

In the following 2 cases the protracted fever caused continued searching in order to eliminate other possible etiologic factors before the diagnosis of neoplasm was made.

Case I.—C. R., male, thirty-seven, American, driver of an ice-cream truck; admitted to the Fifth Avenue Hospital, service of Dr. C. F. Tenney, December 21, 1926.

Chief Complaint.—Languor, cough, and afternoon fever.

Present Illness.—Began six weeks before admission with a dry cough. Three or four weeks after onset he began having fever which came on every day about 4 P. M. and lasted until he fell asleep. He feels languid and has to force himself to do anything. His appetite has been good. He has lost a little weight; his bowels have been regular.

Past History.—He was healthy and strong as a child, though he had the usual diseases. He had an appendectomy at thirteen, a herniotomy at twenty-four, and a repair of the recurrent hernia about eighteen months ago with a marked ventral hernia persisting, for which he wore a belt. No venereal infections.

Family History.—Father died about the age of sixty with chronic alcoholism; mother died while in childbirth at forty-

two. Four sisters are living and well. One brother died in infancy. No history of tuberculosis, cancer, or cardiorenal diseases. Married for sixteen years; has two children living and well.

Physical Examination.—Poorly nourished white man who does not seem acutely ill, and who is mentally alert.

Eyes: Pupils equal and regular; reflexes normal and active; scleræ white and clear; no strabismus; no nystagmus.

Nose: No discharge.

Pharynx: Mucous membranes normal.

Neck: Marked pulsation on right side of neck with a protrusion the size of a marble on coughing which seems to be the carotid artery.

Lungs: Percussion over right apex above third rib is dull; breathing vesicular; no râles.

Heart: No enlargement apparent; rhythm regular; rate 100; sounds are clear; no murmurs; blood-pressure: systolic 110, diastolic 70.

Abdomen: Wears a support; has a large ragged scar in right lower quadrant, with hernia protruding on coughing.

Extremities: Negative; reflexes normal.

On admission the urine was acid; specific gravity, 1.020; albumen, negative; sugar, negative; no casts; a moderate number of white blood-cells. Hemoglobin, 60 per cent.; red blood-cells, 3,400,000; white blood-cells, 14,000; polynuclears, 75 per cent.; lymphocytes, 20 per cent.; transitionals, 3 per cent.; eosinophils, 2 per cent. Urea nitrogen was 13.3 mg. per 100 c.c. of blood; uric acid 2; sugar 111; Wassermann: negative with both alcoholic and cholesterin antigens. Sputum negative for tubercle bacilli.

Course.—On admission *x*-ray of the chest showed a slight increase in the markings about both roots and along the descending bronchi of both lower lobes, but no evidence of infiltration or consolidation in the parenchyma of either lung, and no evidence of fluid. The blood Widal was negative for typhoid or paratyphoid. Blood-culture was reported positive for Streptococcus viridans. At all times careful search showed an ab-

sence of petechiæ and three subsequent blood-cultures failed to confirm the first finding. Gastric contents showed no free hydrochloric acid; total acid 10; occult blood positive. Stool showed no ova or parasites; occult blood positive. Stool was negative for typhoid on two different occasions.

Five days after admission a hard nodule about 1.5 cm. in diameter was found in the left lower anterior cervical chain. The nodule was not tender and seemed fixed to the underlying tissue, but the skin over it was freely movable. *x*-Ray of the upper dorsal and lower cervical spine showed no evidence of any destructive lesion.

At this time fluid was found in the left chest. Tapping of the chest showed a bloody fluid which contained 94 per cent. lymphocytes; 6 per cent. polynuclears. Culture of the fluid showed no growth. The chest fluid was injected into a guinea-pig; the pig was found dead in two weeks, but showed no tuberculosis.

x-Rays of the stomach with barium meal showed no change on January 17, 1927, twenty-seven days after admission. The films made of the colon showed incomplete filling in several areas. It was said that the appearance was not characteristic for malignancy, but the patient was too exhausted for re-examination.

On January 26, 1927 a biopsy was done on the nodule of the neck by Dr. Finsterwald. Transfusion of 500 c.c. was done at the time of biopsy. Dr. Jessup reported that there was a well-defined large round-cell sarcoma and that the normal structure of the lymph-node was lost. The left chest was tapped on five different occasions and the following amounts obtained: 950, 900, 650, 375 c.c. The fifth tapping showed no fluid. Flatness at the base persisted, as did a diffuse shadow in the *x*-ray, so that metastasis was considered the cause.

The patient continued to run a temperature which ranged between 100° to 103° F., during the first two weeks in the hospital, with a slight drop thereafter on a range between 100° to 101.5° F. There was progressive loss of appetite and weight and strength, and there was a marked tendency to cold, clammy perspiration. On January 31, 1927 he began to develop signs of

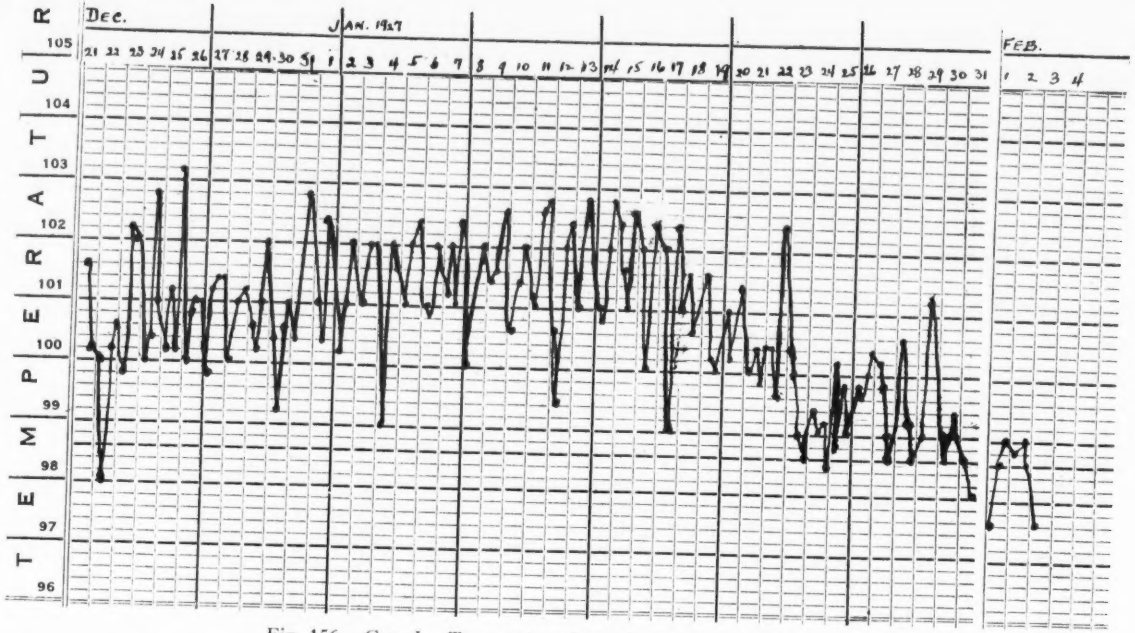

Fig. 156.—Case I. Temperature from time of admission to death.

intestinal obstruction, for which a palliative operation was later done under local anesthesia. The patient gradually became worse, and died February 4, 1927.

Autopsy by Dr. D. S. D. Jessup, February 4, 1927: Male about forty. Frame medium. Rigor mortis present. Edema of right foot and ankle. Considerable emaciation, most marked in trunk and upper extremities. Left side of neck shows a protrusion just above clavicle 3 cm. in size. (This was site of biopsy.) There are two protrusions over sternum. Abdomen much distended and shows a median incision below the navel. This is site of recent operation and closed with silkworm-gut. Right side of abdomen near iliac crest shows an old scar. On opening scar and abdomen the intestines are very much distended. There is some clear yellow fluid. The pelvis is filled with a mass made up of intestines that are matted together by fairly firm new growth. This mass involves the rectum. Scattered through the mesentery of the small intestine are a large number of pale nodules varying in size from 1 to 5 cm. and matting together various loops. At one point this pale growth encircles but does not occlude the gut. The colon shows no involvement of its wall. The caput coli is adherent to the old scar described above, apparently the site of an old operation. The duodenum itself appears to be free, but the wall of the stomach shows new growth in the serosa. Attached to cardiac end of the stomach is a mass 12 x 8 cm. made up of new growth. Retroperitoneally at the tail of the pancreas is another mass. Spleen is 20 x 10 cm. and shows large masses of new growth. Gall-bladder is small. Liver: lower surface of left lobe shows area of new growth. This appears to be in the peritoneum. In other respects the liver shows only congestion. Left kidney, upper pole is adherent to some of retroperitoneal mass. Kidney itself normal in size, markings fair. Right kidney also lies against tumor in its upper pole. On section the upper half is occupied by a tumor mass. The right adrenal is small and thin. Left adrenal can hardly be recognized on account of adherent tumor masses.

Left lung collapsed, adherent to the parietal wall posteriorly and above with very firm adhesions. The lung itself is very firm

and meaty, showing at base new growth in the pleura forming a band 1 cm. in thickness. Right lung, slight adhesions at one point. On section shows congestion and edema. Mediastinum, hard deposits of new growth. Heart, moderate in size. There is some soft red tissue adherent and one of the mitral cusps has the appearance of vegetation. Heart muscle has brownish appearance.

Anatomic Diagnosis.—Retroperitoneal sarcoma, with metastasis in intestine, spleen, kidney, lung, mediastinum, and cervical nodes.

Microscopic Diagnosis.—Large round-cell sarcoma of intestine, spleen, kidney, pleura, peritoneum, diaphragm, retroperitoneal nodes, and mediastinal nodes.

Case II.—K. M., female, American, aged sixty-three, consulted me January 4, 1929.

Chief Complaint.—Pain in lumbar region, four months' duration.

Present History.—Pains in sacral and lumbar regions, coming on only with exertion, but severe on arising after reclining. Eats well, but losing weight for past six months. Slight cough present only at times. Dyspnea only on marked exertion. Bowels regular. Frequency of urination: day, every two hours; night, eight to ten times, but no burning.

Past History.—Has always been well except that she used to have high blood-pressure and some edema of legs. Had hysterectomy for fibroids done in 1908, with cessation of menses since, of course.

Family History.—Husband and four children living and well. One child died of influenza in 1918.

Physical Examination.—Showed a well-nourished woman. Skin clear, but somewhat pale.

Heart: Percussed area of dulness, slightly enlarged to left; action regular, first sound at apex, fairly good muscular quality; at base $A_2 > P_2$. Blood-pressure 175/90.

Lungs: Clear.

Abdomen: Low, median scar; wall soft; no masses felt.

Definite tenderness in both costovertebral angles. No tenderness over spinous processes; no limitation of motion of spine.

Urine showed albumen trace; sugar none; pus ++.

On the basis of a tentative diagnosis of myositis and osteo-arthritis of the spine and of pyelitis, bilateral, the patient was put on a treatment of diathermy and salicylates for the osteo-arthritis and of forced fluids and alkali for the pyelitis.

x-Ray, January 22, 1929, showed an osteo-arthritis of the spine and a normal left kidney; the right kidney was normal in position, but the lower pole showed definite enlargement, particularly toward the median line; no calculi were seen.

General improvement followed. The myositis and osteo-arthritis pains were very much less severe. With a shifting from alkali to caprakol, the tenderness ceased in the right costovertebral angle, but continued in the left; the nocturia was less. The blood-pressure dropped to 140/76. Catheterized specimen still showed pus. In March the right kidney was palpable for the first time.

Although the pains in the back were practically gone, there were occasional nausea and vomiting; the appetite was poor; the bowels costive. Nocturnal frequency persisted, though not so marked. There were occasional headaches; occasional coughing, at times with blood-tinged sputum; night-sweats were frequent and severe and loss of weight continued. The kidney mass in the right upper abdomen became quite distinct, but there was no tenderness, and finally the patient consented to come to the hospital for observation. She was admitted to the Fifth Avenue Hospital, March 18, 1929.

Physical examination at this time showed marked pallor of skin and mucous membrane, but no lemon-yellow tint, and no atrophy of lingual mucosa. There were no enlarged lymph-nodes. The heart was not enlarged; its rate was somewhat rapid but rhythmic; at the apex the first sound was of fairly good muscular quality; at the base over the pulmonic area the first sound was accompanied by a creaky, leathery murmur which was heard less loudly down the left sternal border. The lungs were resonant throughout, the breath sounds vesicular, and there

were a few crepitant râles at both bases posteriorly. The abdomen was somewhat distended. There was a low median linear scar. The right kidney was palpable in part; it could be felt bimanually and seemed to be nodular and about 10 to 12 cm. in diameter. There was no tenderness in the costovertebral angles.

Urine: Acid, specific gravity 1.005; albumen faint trace; sugar none; W. B. C. ++ clumped, R. B. C. occasional. Culture showed many bacteria (B. coli), but smears showed no tubercle bacilli. Catheterized specimens from the ureters showed no essential difference except that the right was quite bloody.

Hemoglobin, 64; R. B. C., 2,700,000; W. B. C., 6300; P. 71; L. 28; M. 1. Urea N. 13.2; sugar 76.9 mgm. per 100 c.c. blood. Icteric index 5.5. Blood-culture: No growth. Widal negative for typhoid bacilli and paratyphoid A and B. Stool negative for bacilli of typhoid group.

Cystoscopic examination by Dr. S. A. Thompson showed bladder mucosa was normal and the capacity approximately normal. The two ureteral orifices were normal in size, shape, and position, but the urine emitted from the right was reddish brown. Catheters were passed on each side without meeting any obstruction. Indigocarmin appeared on left side in four minutes very strongly; on right side in four minutes, but very faintly and continued faintly. Sodium iodid solution was injected into right pelvis, which took 18 c.c.

x-Ray examination of the gastro-intestinal tract was negative except for numerous diverticulæ in descending colon and sigmoid. The duodenum was displaced forward by the retroperitoneal mass. The gall-bladder was normal even with dye. The lower half of the right kidney was definitely enlarged and distorted in shape. The pyelogram revealed that the right pelvis was not dilated, but was located near the upper pole, the calices being normal.

The patient remained in the hospital for four days and then insisted on leaving. During this period the temperature curve was of the hectic type, being low, 97.4° F., in the morning, and high, up to 103° F., in the afternoon.

After reaching home the fever continued its afternoon rise, and there persisted the slight intermittent cough, the irregular vomiting. There was gradually increasing loss of strength. Finally the patient consented to re-enter the hospital May 1, 1929. For the next nine days her temperature ranged between 97° and 102° F., the lowest recorded afternoon temperature being 100° F. On readmission the blood showed hemoglobin 55; R. B. C., 3,800,000; W. B. C., 9400; P., 76; L., 23; M., 1.

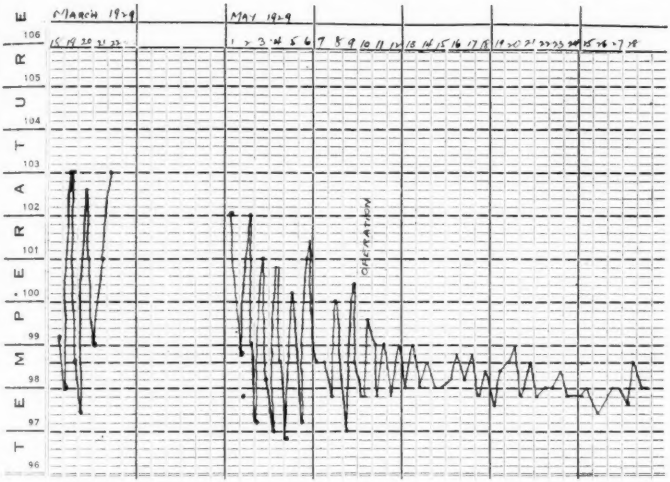

Fig. 157.—Case II. Patient ran fever from March 18th until May 10th, when operated. The period between March 22d and May 1st, while patient was at home, is not shown. After operation the temperature never went above 99° F.

The phenolsulphonephthalein test was 42 per cent. plus 24 per cent., a total of 66 per cent. for the two hours. The urine remained as on the previous admission. *x*-Ray of lungs and of long bones showed no metastases. On May 8th transfusion of whole blood was done by Dr. Thompson from a like (group two) donor, but was stopped at 360 c.c. on account of a moderately severe reaction.

A diagnosis of hypernephroma of the right kidney being

made, Dr. Thompson and Dr. Furness, who concurred, did a right nephrectomy through an anterior approach under spinal anesthesia with neocain.

"The lobulated and capsulated mass measured 13 x 11 cm. Along one edge it showed the structure of a kidney 12 cm. long. On section, this kidney showed opposite the pelvis a projecting spherical growth 10 cm. in diameter. This was covered by a thin capsule and was composed of soft, pale homogeneous material which cut like brain and showed extensive hemorrhage and degeneration. Microscopically the tumor showed alveolar spaces filled by large cells with a clear cell body and a large vesicular nucleus. These groups of alveoli were invading the parenchyma of the kidney outside the solid tumor growth. There were many large thin-walled blood-vessels in the tumor; also areas of necrosis and hemorrhage. Diagnosis: Hypernephroma of kidney" (Dr. D. S. D. Jessup).

After the day of operation the temperature never went above 99° F. The patient made an uneventful convalescence and was discharged cured May 28, 1929.

Wunderlich[1] in 1856, speaking of carcinoma of the stomach, mentions that fever may be present, at times even from the onset, and that the fever may be of a continued or intermittent type. He felt that the fever hastened the loss of weight and indicated an early end. Hampeln,[2] in 1884, cited in detail 2 cases of carcinoma of the stomach, one with metastases and the other without, that ran an intermittent fever for several months with paroxysms accompanied by chills at irregular intervals. Quinin was administered in one case ineffectually. Autopsy showed no inflammatory complications, so that Hampeln suggested the name of "intermittent carcinoma fever." In a third case, with carcinoma of pylorus, Hampeln[3] observed an intermittent fever for four months with irregular rises that ranged as high as 107.6° F. followed by sweating and a fall to normal. Autopsy showed a few metastases in adjacent nodes. Stetter[4] described a case of carcinoma of kidney that ran a high temperature for two months before operation, the fever being 102.2° F. or higher every evening. After operation the temperature was practically normal

for ten days, when pericarditis set in. Marsh[5] cited a child of nine years whose temperature ranged between normal and 102° F. The right kidney was swollen and the case regarded as a perinephritic abscess, but autopsy showed a sarcoma of the kidney. He cited two other cases, both with sarcoma of femur, that ran a fever, one of 102° F., the other of 103° F. He felt that, "In all these cases the elevation of temperature was probably due to tension dependent on the rapid growth of the tumor. Such examples will serve to show that in doubtful cases a high temperature cannot be relied on to prove that a disease is inflammatory rather than malignant." Finlayson[6] cited a case of carcinoma of the stomach with metastases to liver that ran a fever, as well as another case with a temperature between 99° to 100° F. that was taken at first for an abscess of the kidney. He stated that "rapidly growing and rapidly diffused cancers were often associated with a distinct but moderate pyrexia." Kobler[7] reviewed the German literature and mentioned 5 autopsied cases of Kast[8] with carcinoma of the stomach of various sizes, one with metastases to the liver, in all of which intermittent fever was present, sometimes with chills, and in none of which was found any other cause for the fever. Kobler also mentions a case of carcinoma of the pancreas with icterus, reported by Janicke,[9] with fever and chills. Here again at autopsy no other condition was found but the pancreatic carcinoma. Kobler also cites Anker's case,[10] a carcinoma of the stomach with very many metastases and no evidence of inflammation, in a woman of fifty-four with the same course of chills and fever. Kobler's own case ran a hectic fever up to 104.5° F. and showed at autopsy carcinoma of the pancreas, but there was a peritonitis which he thought was only terminal. Völckers[11] described a case of sarcoma of the retroperitoneal nodes in a man of thirty who ran a slowly rising and sinking fever. Puritz[12] presented a case of extensive sarcomatosis of the liver which was greatly enlarged, where the patient ran an irregular fever. He considered the process infectious because of the fever.

In 1889 Freudweiler[13] emphasized the importance of the recognition of fever as an accompaniment of carcinoma of the

stomach. He reviewed 475 cases of carcinoma from the Zürich Clinic from 1884 to 1897. Of the 475 cases, all but 40 were of the gastro-intestinal tract, the majority of carcinoma of the stomach. Of these 475 cases, 24.6 per cent. showed fever which he could not explain except on the basis of the carcinoma. If, however, one omits those cases which showed only isolated temperature rises which lasted only a day or two, there are left only 72 cases, or 15 per cent., of the series. Of these, continued fever occurred in 7 cases (1.5 per cent.), remittent or intermittent fever in 48 (10.1 per cent.), and malaria-like paroxysms in 17 (3.6 per cent.). Excluding the cases with isolated temperature rises and recasting the figures, one finds that the highest percentage is of the group with carcinoma of the liver and biliary tract, 26.3 per cent., and of the group of colon, sigmoid, and rectum, 25 per cent. Of the stomach group and of the group of pharynx, esophagus, and cardia, the figures are 13.5 per cent. and 12.4 per cent. respectively. Of 64 autopsied cases with fever, 50 showed ulceration and 14 showed no ulceration.

Israel[14] in 1896 reported that of 17 malignant tumors of the kidney, one case, a sarcoma, had a hectic fever, which he thought due to absorption of the metabolic products of the tumor, especially as the tumor invaded the renal vein The temperature rose again after operation, when a recurrence took place in the wound, proof that the fever was due to the growth of the tumor.

Karsner[15] mentioned several of his cases of carcinoma in early life as having pyrexia for a time. One girl of ten had carcinoma of rectum with fever considered due to tuberculous peritonitis. Israel[16] in 1911 reviewed 146 cases of malignancy of kidney which he had seen in sixteen years; of these, 18 cases ran fever due only to the tumor of the kidney. Of these 18 cases he operated on 12, or 8.2 per cent., of the total cases. He mentioned one febrile case where the left-sided kidney tumor was taken for a malarial spleen. Another case was treated for occult tuberculosis. Fever in the final cachectic stage with metastases he considered unimportant, as no mistake in diagnosis was likely. Much more important was the fever which came before

the evidence of any growth. He divided the fevers into initial, final, and intercurrent. He distinguished between (1) intermittent or hectic type which may continue for months without a break, as in one case where it lasted for nine months until operated on; (2) recurrent, with alternating periods, febrile and afebrile; (3) fever due to and following hematuria. He stressed the importance of the fever as the initial symptom in some cases, as in one where it was present for twenty-one months, the right-sided mass being mistaken for a gumma of the liver. He felt that fever is a product of malignancy independent of the special histology or of any secondary changes like necrosis from regressive change or destruction by micro-organisms. The fever-provoking substance comes either from the rapidly growing tumor cells or from the normal cells that are being destroyed. He considered fever a bad prognostic sign.

Berg[17] noted temperature elevation whenever a large tumor was present, especially when the latter had grown rapidly. He ascribed the fever either to hemorrhage into the tumor or to the absorption therefrom into the circulation of necrobiotic matter. Longhnane[18] reviewed 35 cases of renal sarcoma in children under twelve years; he found that slight temperature of 99° to 101° F. was the rule in most cases. With metastases to the lungs pyrexia became more marked. Federoff[19] found fever in 25 per cent. of 42 cases of solid kidney tumors that he operated on. Alleman and Bayer[20] observed fever in 5 cases of kidney tumors, some with chills and some without. In some cases the fever was associated with hematuria, but in some cases there was no apparent cause.

Briggs[21] cited a series of 238 cases of various carcinomas, of which 38.2 per cent. showed fever not due to complications, but in only 2.9 per cent. did the hyperpyrexia become a symptom of importance. He felt that the occurrence of metastases had no effect on fever, and that ulceration did not increase the liability to fever except by local inflammation and infection. In one of 3 cases he reported[22] the patient, with carcinoma of lungs, ran a fever curve resembling that of tuberculosis. Briggs[23] quoted Pedrini[24] to the effect that cancers of the liver and of the pleura

were more apt to show fever than the others. Briggs, of his 238 cases of variously situated carcinoma reviewed, found fever in 91, or 38.2 per cent. If one excludes, however, the cases where the temperature rises were isolated and of unimportant duration, the cases with fever are reduced to 32, or 13 per cent., of the total. These corrected figures show fever in 26 per cent. of the liver and gall-bladder cases, 20 per cent. in the lungs and pleura, 19 per cent. in the esophagus, 16 per cent. in the stomach, which compare closely with the figures I corrected from Freudweiler's statistics. Of Briggs' 19 cases of colon and rectum, 5.3 per cent. showed fever, as against Freudweiler's 25 per cent. for colon, sigmoid, and rectum. Briggs found that the cases with metastases showed no great variation from the total number as far as fever was concerned.

Nicholson[25] reported a case of a woman of thirty-eight who ran a fever that mounted up to 100° or 102° F. regularly every afternoon for twenty months. She had intermittent abdominal pain and general weakness, and was diagnosed as endocarditis and Hodgkin's at various times. Autopsy showed renal carcinoma with secondary growths in opposite adrenal, spleen, liver, and lungs.

Finally Creevy[26] presented 2 cases of nephroma, one of whom ran a fever between 100° and 102° F. for two months in the hospital before being operated on for a supposed infected hydronephrosis. Nephrectomy was done for a malignant nephroma, but the patient died in four hours. Autopsy showed tumor growth in the renal vein, but no metastasis. The second case had a nephrectomy done for a malignant nephroma. There had been a flare-up of temperature before operation, but this fever had been ascribed to a post-cystoscopic reaction. Five days postoperatively fever of 104° F. set in and lasted for sixteen days, gradually falling to normal. There was evidence of metastasis in the skull and lung. Despite irradiation, he later developed flaccid paraplegia and died about fourteen months after operation. For three months before death his temperature varied between 96° and 104° F. Creevy refers to the 6 cases of nephroma reported by Castano and Risolia.[27] Three of these

had fever, 2 with chills. In all 3 fever was the initial symptom. In all 3 fever ceased after nephrectomy. Creevy believes that the fever is due to some abnormal substance produced by the tumor cells, and refers to Israel's term of "pyrogenic substance."

Comment.—By this rapid survey of the literature it is apparent that fever may arise from any type of malignant growth, and in the 2 cases here presented, one of retroperitoneal sarcoma, the other of hypernephroma, this experience is further borne out. The nature of the pyrogenic substance gives interesting food for conjecture. Certainly most experiences recorded show that metastasis and tumor necroses and hemorrhages play no deciding rôle in the formation of this fever-provoking substance. It seems to me that if this substance were produced by the tumor cells fever would be much more common than it is. Again, the fact that fever may accompany tumors of such varied natures, such varied histology and biochemistry, would argue for the formation of this pyrogenic substance from the patient's normal cells where they are crushed and invaded by tumor. It seems to me that it is with the most rapidly growing tumors, especially if they are rapidly invading normal tissue or are invading tissue confined in an inelastic capsule, that fever arises. This hypothesis was suggested by Israel and implied by Marsh. The altered body protein produced by pressure of the tumor cells would cause temperature rises even as the protein bacterial endotoxins were shown by Vaughn to be the cause of the infectious fevers.

Conclusions.—1. Two cases of malignancy are cited, one of retroperitoneal sarcoma, the other of nephroma. In both of these fever was most prominent as a symptom, and in both of these careful search had to be made to exclude other causes and to establish malignancy as the true cause of the fever.

2. In all cases of continued fever of obscure origin malignancy must be kept in mind as a possible cause.

3. It is strongly urged that the cause of the fever lies in the altered body protein of the organs cells as they are crushed by the invading tumor.

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